

FDA Executive Summary

Prepared for the
October 9, 2014 Meeting of the
Circulatory System Devices Panel

Classification of More-than-Minimally
Manipulated (MMM) Allograft Heart Valves

Table of Contents

1.	Introduction	4
1.1.	Current Regulatory Pathways	4
1.2.	Device Description	5
2.	Regulatory History	5
3.	Indications for Use.....	5
4.	Clinical Background.....	6
4.1.	Replacement Heart Valves	6
4.1.1.	Prosthetic (Non-Allograft) Heart Valves	6
4.1.2.	Allograft Heart Valves	6
4.1.3.	MMM Allograft Heart Valves	7
4.2.	Current Standard of Care	7
5.	Literature Review on MMM Allograft Heart Valve Devices	8
5.1.	Methods	8
5.2.	Results	9
5.2.1.	Safety	10
5.2.2.	Effectiveness.....	11
5.2.3.	Immune Response.....	12
5.3.	Limitations.....	14
5.4.	Overview of the Published Literature	16
6.	Reports on Other MMM Devices.....	16
7.	Risks to Health Identified Using “Manufacturer and User Facility Device Experience” (MAUDE) Database	17
7.1.	Overview of MAUDE Database	17
7.2.	MAUDE Search Results: MMM Allograft Heart Valve Devices.....	18
7.2.1.	Discussion of Events – SG Pulmonary Valves	20
7.2.2.	Discussion of Events – SG Aortic Valves	22
7.2.3.	Time to Events after Implantation – SG Pulmonary Valves	23
7.2.4.	Time to Events after Implantation – SG Aortic Valves	23
7.2.5.	Summary of the MDR Review	24
8.	Summary	24
8.1.	Reasonable Assurance of Safety.....	25
8.2.	Reasonable Assurance of Effectiveness	26
8.3.	Overview of Proposed Classification	27
9.	References	30
Appendix A: Database Search Queries and Results – Search 1		33
Appendix B: Database Search Queries and Results – Search 2		34
Appendix C: Public MAUDE Information on MMM Allograft Heart Valve Medical Device Reports (MDRs).....		35

List of Tables

Table 1: 510(k) clearance for MMM allograft heart valve	5
Table 2. Reported Problems and TTEO – SG Pulmonary Valves (28 MDRs)	23
Table 3. Reported Problems and TTEO – SG Aortic Valves (26 MDRs)	24
Table 4. Pre-Market and Post-Market Requirements for 510(k)s and PMAs	28

List of Figures

Figure 1: Year MDR received by FDA – SG Pulmonary Valves	19
Figure 2: Year MDR received by FDA – SG Aortic Valves	20

1. Introduction

Per Section 513(b) of the Food, Drug, and Cosmetic Act (the Act), the Food and Drug Administration (FDA) is convening the Circulatory System Devices Advisory Panel (the Panel) for the purpose of obtaining recommendations regarding the classification of more-than-minimally manipulated (MMM) allograft heart valves, a device type which remains unclassified. Specifically, the FDA will ask the Panel to provide recommendations regarding the regulatory classification of MMM allograft heart valves. The Panel will also be asked to discuss whether this device type fits the statutory definition for a Class III device.

FDA is holding this panel meeting to obtain input on the risks to health and benefits of MMM allograft heart valves. The Panel will discuss whether MMM allograft heart valves should be classified into Class III (subject to Premarket Approval), Class II (subject to General and Special Controls) or Class I (subject only to General Controls). If the Panel believes that classification into Class I or II is appropriate for MMM allograft heart valves, the Panel will also be asked to discuss appropriate controls that would be necessary to mitigate the risks to health.

FDA proposes classification of MMM allograft heart valves into Class III because they are life-sustaining devices for which insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of safety and effectiveness. Specifically, only one MMM allograft heart valve has been cleared and the scientific methods for processing and assessing MMM allograft heart valves are relatively novel. As such, there are not well-established scientific methods to evaluate decellularization processes, to conduct *in vitro* evaluations (e.g., tissue mechanical properties, valve durability), or to evaluate *in vivo* recellularization. New types of safety and effectiveness concerns (including incomplete or variable decellularization (affecting antigenicity and calcification), limited *in vivo* recellularization (affecting valve structural integrity and dimensional stability), and extracellular matrix structural deterioration) preclude the Agency the ability to develop special controls to address these issues. The manufacturing and processing of the MMM is critical and has a global effect on the valve tissue, impacting the hydrodynamic performance, structural integrity, durability, and immunogenicity of the valve. As a result, CDRH believes that premarket review of these manufacturing processes are needed. Additionally, the risks to health were confirmed via a systematic literature review and MDR search to be consistent with other non-allograft replacement heart valves, all of which are regulated as Class III devices.

1.1. Current Regulatory Pathways

The FDA determined that MMM allograft heart valves were substantially equivalent to traditional, cryopreserved allograft heart valves (non-MMM allograft heart valves) which were marketed in the US before passage of the Medical Device Amendments on May 28, 1976 (i.e., pre-amendments devices). Because the MMM allograft heart valves have not been formally classified, the FDA reviews these devices via the premarket notification (510(k)) pathway until the classification process is completed. To date, the FDA has cleared one (1) MMM allograft heart valve from one (1) manufacturer.

1.2. Device Description

An MMM allograft heart valve is a human valve or valved-conduit that has been aseptically recovered from qualified donors, dissected free from the human heart, and then subjected to a manufacturing process (or processes) which alters the original relevant characteristics of the tissue (21 CFR 1271.3(f), 21 CFR 1271.10(a)(1), and 21 CFR 1271.20). The valve is then stored until needed by a recipient. An example of such a manufacturing process is one which intentionally removes the cells and cellular debris, with the goal of reducing *in vivo* antigenicity. The MMM allograft heart valve is intended to perform the function of any of the heart's natural valves.

2. Regulatory History

The clearance of the MMM allograft heart valve via the 510(k) process was based on evidence that a similar device (i.e., non-MMM allograft heart valve) was in interstate commerce, and labeled for a specific intended use prior to passage of the Medical Device Amendments on May 28, 1976. As such, the 510(k) cleared device, the CryoValve® SG Pulmonary Valve and Pulmonary Valve Conduit, was determined to be substantially equivalent to the pre-amendments non-MMM allograft heart valves. The CryoValve® SG Pulmonary Valve and Pulmonary Valve Conduit is a human valve or valved-conduit that has been aseptically recovered from qualified donors, dissected free from the human heart, and then subjected to a manufacturing process (the SynerGraft (SG) process) intended to remove the cells and cellular debris for the purpose of reducing antigenicity. The SG-processed valve is a decellularized version of the firm's CryoValve® Human Heart Valve which is a standard, cryopreserved human heart valve (i.e., the pre-amendments, non-MMM allograft heart valve).

Note that as of May 25, 2005, non-MMM allograft heart valves are regulated solely as tissue products within the Center for Biologics Evaluation and Research (CBER), under 21 CFR 1271, following the codification of FDA's tissue regulations. Since this initial clearance, there have been no other subsequent clearances for any other MMM allograft heart valves via the 510(k) process. Please refer to Table 1 below for additional information associated with the clearance of the MMM allograft heart valve device:

Table 1: 510(k) clearance for MMM allograft heart valve

Manufacturer	Device Name	510(k) Number
CryoLife, Inc.	CryoValve® SG Pulmonary Human Heart Valve (Model SGPV10) and CryoValve® SG Pulmonary Human Heart Valve and Conduit (Model SGPV00)	K033484 K083106 (revised description to include immunogenicity claim) K092021 (extended shelf life)

3. Indications for Use

The Indications for Use statement identifies the condition and patient population for which a device should be appropriately used. Proposed Indications for Use, consistent with the indications for the device noted in Table 1, are as follows:

[This device] is indicated for the replacement of diseased, damaged, malformed, or malfunctioning native or prosthetic [position] valves.

4. Clinical Background

This section summarizes the history of heart valve replacement procedures, along with specific use of MMM allograft heart valves in conjunction with these procedures.

4.1. Replacement Heart Valves

Replacement heart valves are used to replace malfunctioning native heart valves and may include transplanted human heart valves (i.e., allograft heart valves and MMM allograft heart valves) or non-allograft, prosthetic valves. The construction and uses of prosthetic heart valves, allograft heart valves, and MMM allograft heart valves are varied, as described in the following sections.

4.1.1. Prosthetic (Non-Allograft) Heart Valves

Prosthetic heart valves may be constructed of biological materials (e.g., porcine, bovine, equine valves or pericardial tissue) or prosthetic materials, or some combination of the two. Valves constructed solely of prosthetic materials are termed mechanical valves, while those which include biological materials are termed bioprosthetic (or tissue) valves.

The first mechanical heart valve was non-orthotopically implanted in the descending aorta by Dr. Hufnagel in 1952 (Garcia, 1981). Subsequently, the Starr-Edwards Silastic Ball Valve (mechanical heart valve), a “ball and cage” design, was implanted in 1960. Thereafter, a tilting-disc (or mono-leaflet) design entered the market, followed by bileaflet designs, which are the predominant design for mechanical heart valves today.

The first bioprosthetic heart valves were implanted in the 1960s. Bioprosthetic valves may consist of whole valves transplanted from another species (e.g., porcine valves) or may consist of assembled valves, constructed of tissues from another species (e.g., bovine pericardium). Bioprosthetic valves are treated with solutions to bind the tissues to eliminate an immune response, to reduce *in vivo* calcification, and to sterilize the valve. The valves are stored in a storage solution until needed and then rinsed prior to implantation.

All non-allograft heart valves are classified as Class III devices under 21 CFR 870.3925.

4.1.2. Allograft Heart Valves

Allograft heart valves are human heart valves or valved-conduits that have been aseptically recovered from qualified donors, dissected free from the human heart, and then stored until needed by a recipient. The allograft heart valve replacement dates back to the 1960s.

In 1994, the FDA ruled (per 59 FR 52078) that allograft heart valves marketed on or before June 26, 1991 were substantially equivalent to pre-amendments replacement heart valves (i.e., medical devices) and were subject to general controls and FDA inspection. Following promulgation of FDA's tissue regulations, the regulatory authority for allograft heart valves transferred to CBER on May 25, 2005 (69 FR 68612), and allograft heart valves are presently regulated solely as tissue products (instead of medical devices). The regulation of tissue products focused on the establishment of donor eligibility procedures, current good tissue practices, and other procedures to prevent the introduction, transmission, and spread of communicable diseases (21 CFR 1271.1(a)).

4.1.3. MMM Allograft Heart Valves

MMM allograft heart valves are allograft heart valves which have been more-than-minimally manipulated. The term "minimal manipulation" means "processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement" (per 21 CFR 1271.3(f)). As such, MMM allograft heart valves are allograft heart valves that have been subjected to a manufacturing process (or processes) which alters the original relevant characteristics of the tissue (21 CFR 1271.3(f)). Human-tissue-based products that have been determined to be more-than-minimally manipulated may be subject to additional regulatory controls, such as pre-market review. MMM allograft heart valves are regulated as medical devices subject to the regulatory authority of the Center for Devices and Radiological Health (CDRH), per 21 CFR 1271.10(a)(1), and 21 CFR 1271.20. At this time, such devices remain unclassified in CDRH.

However, one MMM allograft heart valve is cleared in the US as a device intended for use in heart valve replacement procedures; this clearance is limited to the pulmonic indication only. The FDA granted this clearance through the 510(k) process based on documentation that demonstrated that the MMM allograft heart valve was substantially equivalent to non-MMM allograft heart valves which were in commercial distribution prior to passage of the Medical Device Amendments on May 28, 1976. Clinical evidence regarding this use, however, particularly long-term performance, remains limited. A voluntary post-clearance study is presently ongoing with a projected completion in 2014.

4.2. Current Standard of Care

It is estimated that more than five million Americans are diagnosed with heart valve disease each year (Nkomo et al., 2006). The prevalence of heart valve disease varies across the four valves, with aortic and mitral disease being most prevalent. Treatment options for malfunctioning heart valves include medical management, valve-repair, and valve replacement (either surgical or transcatheter), with any of the aforementioned heart valves (i.e., prosthetic, allograft, or MMM allograft), or with an autograft (a patient's own valve).

Prosthetic heart valves are often the valve replacement option of choice for adults. Mechanical heart valves offer a longer lifetime, as compared with bioprosthetic valves, but require lifetime antithrombotic medications. Prosthetic heart valves are generally not intended for pediatric patients (age < 22 years old as defined by FDA); however, their labeling is not restricted to only adult patients and there are some such valves that are manufactured in sizes that can accommodate pediatric patients, most often larger-sized or older pediatric patients.

Allograft heart valves are often more readily available in the smaller sizes needed by pediatric patients and do not require lifetime antithrombotic medications. However, allografts are known to stimulate a donor-specific humoral response in recipients, as indicated by elevated panel reactive antibody (PRA) levels post-implant. Such allosensitization may lead to accelerated degeneration of the valve, requires the use of lifetime immunosuppressive medications, and results in an increased PRA with decreased number of possible solid organ transplant donors (if needed), with an associated longer period of time on transplant waiting lists, and the increased risk for early solid organ failure and reduced patient survival after transplant. The use of immunosuppressants is particularly concerning for very young pediatric patients (i.e., neonates, infants, and toddlers) since such reduced immune response places them at significantly greater risk for acquired infections and illnesses just at a time when they are highly predisposed (e.g., due to crawling, sharing toys, teething) to exposures to such pathogens.

MMM allograft heart valves could potentially be manufactured to reduce *in vivo* antigenicity and calcification, to increase durability, and to achieve novel functionality, including recellularization and host adaptation (i.e., grow with the patient). However, only one such device has been marketed in the US (i.e., CryoValve® SG Pulmonary Valve and Conduit). As such, clinical data are limited, both in numbers of patients and in duration of follow-up. While a voluntary post-clearance study of the CryoValve® SG product is being conducted, the study has not yet been completed (projected completion in 2014). As compared with prosthetic heart valves, these devices pose the additional risk of disease transmission and infection, as they are not sterile devices.

5. Literature Review on MMM Allograft Heart Valve Devices

FDA has conducted a systematic literature review in an effort to gather any published information regarding safety and effectiveness of MMM allograft heart valves for use in heart valve replacement procedures.

5.1. Methods

FDA conducted a systematic literature search to identify any relevant references published from January 1, 1990 (ten years prior to US commercialization of first known MMM allograft heart valve) up to and including November 18, 2013 (date of the last search). We searched three electronic databases (PubMed, Embase, and Web of Science) using two sets of search terms:

Search 1: “allograft heart valves” or “cryo valve” or “synergraft”, which yielded 59 articles in Pubmed, 90 articles in Embase, and 86 articles in Web of Science (Appendix A). After removing 59 duplicates, a total of 90 articles remained for further screening.

Search 2: “Homograft heart valve” NOT (“allograft heart valves” or “cryo valve” or “synergraft”). This yielded 23 additional results in Pubmed, and no additional results in Embase or Web of Science (Appendix B).

The searches were limited to publications in English. After results from each set of search terms were combined and duplicate references were removed, this search yielded a total of 113 results. Following a review of the titles, abstracts, and the full articles, 92 articles were excluded as they were not relevant to the topic at hand (e.g., pertained to engineering or device design only, non-systematic review, not original clinical research study, lab/in vitro research, etc.). FDA reviewed the remaining 21 articles in greater detail.

5.2. Results

Of the 21 articles, 10 were prospective cohort studies and 11 were retrospective cohort studies, including some retrospective analysis of explanted heart valves. No randomized controlled studies were found. Twelve studies were conducted in the US, mostly in one single center/hospital per each study; the rest of the studies were conducted in Germany (4 were conducted by the same group in Lubeck), Australia, Norway, and Switzerland.

Fourteen of the aforementioned 21 articles involved the decellularized MMM allograft heart valves (“subject” valves; namely, the cleared pulmonic valves as well as the aortic valves which have not received FDA clearance or approval), 11 of which involved concurrent and/or matched controls within the same study (“control” valves; namely, the standard, cryopreserved allograft heart valves), and 3 of which involved no controls; the remaining 7 articles involved studies of the control allografts only.

The 11 articles that involved both the decellularized MMM allograft heart valves and the standard, cryopreserved allograft heart valves were the most relevant for the purpose of our literature review because those were the only articles that compared the two devices in equivalent populations using similar methodologies over the same time period. Those articles are therefore the main focus of this review, while the decellularized MMM-only or standard allograft-only studies are provided mainly as a background reference.

Studies that were sponsored by the MMM allograft manufacturer (CryoLife, Inc.) or for which the investigator(s) had a financial conflict of interest are denoted with an asterisk (*). Of the nine studies conducted in the US, five (5) of the studies were funded fully or partially by the MMM allograft heart valve manufacturer (CryoLife,

Inc.), and based on the information provided a sixth study may have been funded fully or partially by the MMM allograft heart valve manufacturer.

5.2.1. Safety

Most studies that compared the decellularized MMM allograft heart valves with standard, cryopreserved allograft heart valves did not assess valve-related adverse events (AEs). Overall, AEs were rare or infrequent (Bechtel *et al.*, 2003; Zehr *et al.*, 2005; Sievers *et al.*, 2003; Konuma *et al.*, 2009*; Hawkins *et al.*, 2003) and did not differ between the subject and control valves (Brown *et al.*, 2010*; Brown *et al.*, 2011*; Dohmen *et al.*, 2007; Tavakkol *et al.*, 2005). Across all 21 studies, the following nine (9) adverse events were reported and mostly showed non-significant differences between groups. Although many of the studies were not powered to detect statistical significance, a significance difference is stated below whenever available.

1. Death or valve-related death/survival: All studies reported either no valve-related death or operative death (Sievers *et al.*, 2003; Brown *et al.*, 2011*; Burch *et al.*, 2010; Elkins *et al.*, 2001*) or no significant difference in death/survival (Betchel *et al.*, 2008; Tavakkol *et al.*, 2005; Ruzmetov *et al.*, 2012*; Konuma *et al.*, 2009*). For example, one study reported possible subject valve-related late death (1.2% [4/342]) was slightly higher (no test of significance was provided) than definite valve-related death in the control group (0.8% [10/1246]). However, the overall survival was not significantly different between subject and control groups when the analysis was adjusted by propensity scores (Brown *et al.*, 2010*).
2. Endocarditis or infection of the heart valve: No endocarditis (Zehr *et al.*, 2005) was reported at 6 months of follow-up for the subject valves. No significant differences were found in the rate of freedom from endocarditis (100% vs. 99.3%) between subject and control groups at the mean follow-up of 5 years (Brown *et al.*, 2010*).
- 3-5. Thromboembolism, Thrombosis, and Bleeding: No thromboembolism (Zehr *et al.*, 2005) was reported for the subject valves at 6 month follow-up. A combined rate of freedom from thromboembolism, valve thrombosis, and bleeding were not significantly different between the subject and control groups (98.9% vs. 91.1%) at the mean follow-up of 5 years (Brown *et al.*, 2010*).
6. Reintervention/reoperation (e.g., revision/replacement, explant): No significant differences were found in reintervention/explantation rates between the subject and control groups at mean follow-up periods ranging from 16 months to 5.5 years (Brown *et al.*, 2010*; Brown *et al.*, 2011*; Burch *et al.*, 2010; Tavakkol *et al.*, 2005). However, one study (Ruzmetov *et al.*, 2012*) reported a significantly higher freedom from conduit failure in the subject group (subject 87% vs. control 68%, $p=0.05$) at 10 years.

Ruzmetov *et al.* (2012*) also reported consistent higher freedom from explantation in the subject group compared with the control group at 5 and 10 years (5 years: subject 92% vs. control 77%, $p=0.08$; 10 years: subject 90% vs. control 68%, $p=0.02$, significant at 10 years only).

7. Valve/conduit deterioration: There were very few studies that stated deterioration results. No structural deterioration was found in 11 subject valves at a mean of 4 years post-implant (no control) (Dohmen *et al.*, 2007). However, one study (Ruzmetov *et al.*, 2012*) reported that among the 97 hospital survivors, freedom from conduit dysfunction was significantly worse in the control group (69% and 48% at 5 and 10 years, respectively) as compared with the subject group (82% and 74% at 5 and 10 years, respectively; $p=0.05$). Of note, in some studies, the valve or conduit dysfunction or failure were not specified to be structural or nonstructural. For example Brown *et al.* (2010*) only vaguely reported no valve-related failure. One study stated that no significant differences were found between subject and control groups in terms of nonstructural valve dysfunction (Brown *et al.*, 2010*).
8. Allograft/homograft or aortic wall calcification: No calcification or wall thickening was found in two subject-valve (no control) studies (Dohmen *et al.*, 2007; Zehr *et al.*, 2005), and another study found no significant differences in calcification between subject and control groups (26% vs. 15%, $p=0.31$) (Betchel *et al.*, 2004).
9. Fibroproliferation: One study showed the subject valves to have much more fibroproliferation (42% vs. 18%) than the control valves (Bechtel *et al.*, 2004), but no clinical adverse consequences were apparent from this, and the clinical consequences of this finding are unknown.

5.2.2. Effectiveness

Across all studies, effectiveness was mainly assessed by 1) pressure gradient/stenosis, 2) valve regurgitation, and 3) effective orifice areas (EOA). A summary is provided below for each parameter.

1. Pressure gradient/stenosis: In general, a high pressure gradient is indicative of valve stenosis, which impairs cardiac function. The pressure gradients increased in both subject and control valves after 1 to 6 months post-implant and there was no further increase up to 10 months (Bechtel *et al.*, 2003; Bechtel *et al.*, 2004). Several studies found no significant differences in pressure gradients between subject and control valves at 1, 6, or 10 months (Bechtel *et al.*, 2003; Bechtel *et al.*, 2004; Betchel *et al.*, 2008; Sievers *et al.*, 2003; Tavakkol *et al.*, 2005) or at 4 to 5 years post-implant (Brown *et al.*, 2011*; Burch *et al.*, 2010). Another study found that pressure gradients following Ross procedures were significantly lower for the subject valves compared to the control valves ($p<0.002$) but not significantly different

between the two valve groups following right ventricular outflow tract (RVOT) reconstruction (Brown *et al.*, 2010*). However, at longer (52 months) follow-up, one study found a statistically significant but marginally higher pressure gradient in the subject group compared to the control group (Bechtel *et al.*, 2008).

2. Valve regurgitation/insufficiency: Most studies found either no functional regurgitation at up to 5 years (Dohmen *et al.*, 2007), or no significant differences in regurgitation or insufficiency between the subject and control groups at 4 to 5 years follow-up (Brown *et al.*, 2011*; Burch *et al.*, 2010; Konuma *et al.*, 2009*; Sievers *et al.*, 2003). However, several studies reported seemingly favorable performance in the subject valves. For example, the Brown *et al.* (2010*) study, which included the largest sample size of any study in this review (subject=342, and control=1246) found that pulmonary insufficiency was significantly lower at 4 years in the subject patients compared to the control patients ($p<0.01$) following both Ross and RVOT reconstruction procedures. Tavakkol *et al.* (2005) reported that the subject valves showed less pulmonary insufficiency and stenosis compared to the control valves at 16-21 months post-procedure ($p=0.017$ and $p=0.012$ respectively). With stratification analysis, Konuma *et al.* (2009*) found that freedom from moderate to severe insufficiency ($>3+$) was significantly less frequent for the subject patients than for the control patients ($p=0.05$); and for patients greater than 2 years of age, the subject valves were significantly less regurgitant ($p=0.045$) and stenotic ($p=0.041$) than the control valves.
3. Effective orifice areas (EOA): Pulmonary EOA declined over time in both subject and control valves. The reduction in EOA in the subject valves was found to be either significantly less than in the control valves (Sievers *et al.*, 2003), or not significantly different than in the control valves (Bechtel *et al.*, 2003; Bechtel *et al.*, 2004).

5.2.3. Immune Response

MMM allograft heart valves include those which have been subjected to a decellularization process. The primary purpose of decellularization is to remove potentially immunogenic cells from the valve. This is potentially important, as human leukocyte antigen (HLA) class I and II molecules present on the MMM allograft heart valve could sensitize the recipient to the donor tissue and induce rejection or predispose the valve to accelerated degeneration and failure. Reduced sensitization to HLA molecules is also relevant for transplant recipients, as the presence of antibodies against multiple HLA types (indicated by increased panel reactive antibody [PRA] values) correlates with a decreased number of suitable donors for subsequent organ transplantation. This is especially applicable to the pediatric population which may be hyper-responsive to sensitization following allografts, and may be candidates for future transplant surgery or additional valve replacement.

Eight clinical studies reported immunologic responses. Two compared immunologic responses between the decellularized MMM allograft heart valve (“subject”) and standard, cryopreserved allograft heart valves (“control”; Bechtel *et al.*, 2003; Hawkins *et al.*, 2003), two studied immunologic responses in only the subject valves (Elkins *et al.*, 2001*; Zehr *et al.*, 2005), and the remaining four studied only the control valves (Vogt *et al.*, 1999; Mitchell *et al.*, 1995; Mitchell *et al.*, 1998; Yap *et al.*, 2006). The follow-up times varied among the studies, including follow-up at 3 days, 1 month, 3 months, 6 months, 1 year, and/or beyond 1 year.

For the two studies (Bechtel *et al.*, 2003; Hawkins *et al.*, 2003) which compared immunologic responses in the two groups, the subject valves showed a lower prevalence of anti-HLA antibodies which reached statistical significance, with follow-up ranging from one month to one year. White blood cell counts and C-reaction protein were not statistically different between the two valves in the first three postoperative days (Bechtel *et al.*, 2003).

For the two studies which evaluated the subject valves alone (Elkins *et al.*, 2001*; Zehr *et al.*, 2005), allosensitization was assessed by panel reactive antibody (PRA) assay. The percent of subjects with no detected antibodies was 100% at baseline and decreased to 91% at one month, 88% or 86% (i.e., Elkins *et al.*, 2001* and Zehr *et al.*, 2005, respectively) at three months, and increased slightly to 95% at one year post-implantation (Zehr *et al.*, 2005).

In one study which evaluated the control valves, alone, anti-HLA class I antibodies were detected in 68% of subjects (by CDC testing) and 96% of subjects (by ELISA testing), and anti-HLA class II antibodies were detected in 82% of subjects, at a mean of three years of follow-up (Yap, 2006). However, another two studies evaluated only control valves, finding morphologically nonviable cells, which are unlikely to grow or exhibit active metabolic functions; in these studies, the inflammatory cells were prominent only in infective endocarditis at intermediate-term (2-11 months) explants, and lymphocytes and other inflammatory cells were sparse at long-term (1-9 years) explant (Mitchell, 1998). The authors concluded that the immune responsiveness has little, if any, impact on late allograft function or degradation (Mitchell *et al.*, 1995; Mitchell *et al.*, 1998).

There are demonstrated differences in immunogenicity findings across different valve positions (e.g., pulmonic, aortic) and patient populations (e.g., pediatric and adult). Namely, Elkins *et al.* (2001*) studied the decellularized MMM allograft heart valves implanted in the pulmonary and aortic positions comparing 58 pulmonary valves and 8 aortic valves. They found that the decellularized MMM allograft heart valves implanted in the aortic position had a higher percentage of increased immunoreactivity (67% and 67% of PRA at 1- and 3-month post-surgery, respectively) compared to the decellularized MMM allograft heart valves implanted in the pulmonary position (6% and 8% of PRA

at 1- and 3-month post-surgery, respectively). For different patient populations, Vogt et al. (1999) stated that macrophages and langerhans-cells were found only in the pulmonary allografts of pediatric patients, whereas by contrast, aortic allografts in adult patients showed a limited humoral response.

In summary, the eight (8) studies that involved the assessment of allosensitization are suggestive of reduced immunogenicity for the decellularized MMM allograft heart valve compared to the standard, cryopreserved allografts. The limitations in interpretability of the findings are discussed below.

5.3. Limitations

The aforementioned section presented findings from the systematic literature review of scientific papers evaluating the safety and effectiveness of MMM allograft heart valves. The review focused on the one MMM allograft heart valve that has been cleared by the FDA, the CryoValve® SG Pulmonary Valve and Pulmonary Valved Conduit (CryoLife, Inc.; K033484), and provided comparisons to literature pertaining to standard, cryopreserved, non-MMM allograft heart valves. The presented findings and interpretations must be considered in light of the following key limitations in study design and methodology.

First, all of the 21 studies are observational studies without any randomization, and only 11 of 21 have a concurrent control group. The lack of randomization could cause confounding of the study results if there were differences in the two study populations that affected the clinical outcomes assessed.

Second, many of the studies lack important information on methodology (including inclusion and exclusion criteria) and clinical outcomes. Instead, most articles tended to focus on the heart valve functions, only. This lack of detailed information hinders the interpretation of the study results.

Third, there was a potential for conflict of interest in some of the studies. Of the nine studies conducted in the US, five (56%) of the studies were funded fully or partially by the MMM allograft heart valve manufacturer (CryoLife, Inc.), and based on the information provided a sixth study may have been funded fully or partially by the MMM allograft heart valve manufacturer. None of the additional MMM allograft heart valve studies stated whether they were funded by CryoLife or not. Therefore, caution should be taken in drawing conclusions from studies that showed superior performance of the MMM allograft heart valves compared to standard allograft heart valves.

Fourth, the MMM allograft heart valves and standard allograft controls may not be completely comparable. Specifically, the time period covered for the controls was considerably earlier than for the MMM allograft heart valve group in the largest study in this review (Brown *et al.*, 2010*), so the reportedly favorable performance, safety, and/or immunogenicity results with the MMM allograft heart valves could have been due to differences pertaining to the earlier time periods (for example, concomitant

treatments may have changed over time or differ between institutions, test methods may differ, etc.).

Fifth, most of the studies had small sample sizes, with 15 of the 21 (71%) original studies enrolling less than 50 participants per study arm. When sample sizes are too small they are generally not powered to detect small or moderate differences in performance between treatment groups.

Sixth, fifteen (15) of the 20 (75%) original studies (one is not specified) were conducted at a single clinical site, and some of these were based within the same study site. The small number of different study sites presents a potential problem regarding representativeness of the study samples and, therefore, potentially limits the generalizability of these findings to implanted patients at large.

Seventh, generalization of immunogenicity findings across different valve positions (e.g., pulmonic, aortic, etc.) may be inappropriate, as decellularization processing may have different effects/effectiveness depending on the valve (pulmonic, aortic) being processed and allosensitization within patients may vary depending on position, as well. Namely, Elkins *et al.* (2001*) studied the decellularized MMM allograft heart valves implanted in the pulmonary and aortic positions comparing 58 pulmonary valves and 8 aortic valves. They found that the decellularized MMM allograft heart valves implanted in the aortic position had a higher percentage of increased immunoreactivity (67% and 67% of PRA at 1- and 3-months post-surgery, respectively) compared to the decellularized MMM allograft heart valves implanted in the pulmonary position (6% and 8% of PRA at 1- and 3-month post-surgery, respectively).

Eighth, generalization of immunogenicity findings across different patient populations (e.g., pediatric and adult) may be inappropriate, as allosensitization across these populations may vary significantly. For example, Vogt *et al.* (1999) stated that macrophages and langerhans-cells were found only in the pulmonary allografts of pediatric patients, whereas by contrast, aortic allografts in adult patients showed a limited humoral response.

Finally, some of the reported immunogenicity studies may not have employed techniques which are sufficiently sensitive to accurately detect allosensitization. For instance, Elkins *et al.* (2001*) utilized anti-HLA (human leukocyte antigen) antibodies which might not be a sensitive marker for the alloreactive cells that are likely to be the actual agents of valve deterioration, and may therefore over-predict the potential benefit of the decellularized MMM allograft heart valve (Hogan and O'Brien, 2003). Regarding Bechtel *et al.* (2003), the CDC PRA test used in this case detects only complement fixing antibody against HLA class I, and does not detect antibody to HLA class II. Thus, it is relatively insensitive compared to methods used in the other studies.

5.4. Overview of the Published Literature

This systematic literature review examined the published scientific literature (since January 1, 1990) using very general search terms from the three major databases. It assessed the safety and effectiveness of decellularized MMM allograft heart valves, in 11 cases in comparison with standard, cryopreserved allograft heart valves. Some of these studies reported no significant differences in terms of safety and/or effectiveness endpoints. Others demonstrated apparent safer and better performance of the decellularized MMM allograft heart valves. These mixed study findings need to be considered in light of key limitations in study design and methodology that limit the interpretation and generalizability of the study results. This systematic literature review confirmed the life-supporting, life-sustaining nature of MMM allograft heart valves and that the risks to health of MMM allografts are consistent with other non-allograft replacement heart valves, all of which are regulated as Class III devices. In addition, given the limitations in the published literature (as described in detail in the preceding section), FDA concludes that insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device.

6. Reports on Other MMM Devices

The published literature pertaining to MMM allograft heart valves are necessarily limited by the fact that only one such device has been 510(k)-cleared (i.e., the CryoValve® SG Pulmonary Human Heart Valve and CryoValve® SG Pulmonary Human Heart Valve and Conduit, K033484). As such, a limited (Google) search was conducted for other decellularized products to determine if reports on other MMM devices might provide insights into additional probable risks not identified in the systematic literature review for MMM allograft heart valves. Reports were found for the following MMM devices: a decellularized porcine heart valve, a decellularized femoral vein allograft, and a decellularized bovine femoral-posterior tibial bypass graft. Note that these devices are not cleared in the US; as such, there are no MDR reports. The safety concerns raised within the isolated reports are highlighted below.

Simon *et al.* (2003; AKH University of Vienna, Austria) reported the early failure of a decellularized porcine heart valve in pediatric patients: “The xenogenic collagen matrix of the ... valve elicits a strong inflammatory response in humans which is non-specific early on and is followed by a lymphocyte response. Structural failure or rapid degeneration of the graft occurred within 1 year. Calcific deposits before implantation and incomplete decellularization may indicate manufacturing problems. The [decellularized] porcine ... heart valves should not be implanted at this stage and has been stopped.”

Madden *et al.* (2005; Baystate Medical Center, Massachusetts) reported a comparison of decellularized femoral vein allografts and prosthetic grafts (PTFE) for hemodialysis access. This was a prospective, randomized study which enrolled 27 patients in each arm. The study found that significantly more fistulograms were performed in the decellularized cohort ($p < 0.05$) and there were significantly more access graft failures (i.e., 30% failed in the decellularized cohort versus 18% in the PTFE cohort). The study concluded that “...

our results do not support the routine use of [these] allografts in the general dialysis population.”

Sharp *et al.* (2004; John Radcliffe Hospital, Oxford, UK) reported on the failure of a decellularized bovine ureter used as a femoral-posterior tibial bypass graft in a 68-year-old patient. The article reported: "Our patient [presented] at 8 weeks with aneurismal degeneration along the course of the graft. We urge caution in the use of these grafts until convincing data in humans is presented.”

These articles indicate that decellularization may degrade the structural integrity of the tissue and that MMM allografts may present increased risk of structural valve deterioration and aneurismal degeneration as compared with standard, cryopreserved allografts.

Additionally, the following article presents interesting information regarding the potential for thrombus formation on decellularized allograft heart valves. Namely, Stam *et al.* (2004) concluded that cell removal impairs the physical properties of the valve structure (porcine aortic valves) and exposes bare collagen fibers that are highly thrombogenic. As such, MMM allografts may also present increased risk of thrombus, thromboembolism, stroke, and renal insufficiency/failure as compared with standard, cryopreserved allografts.

7. Risks to Health Identified Using “Manufacturer and User Facility Device Experience” (MAUDE) Database

7.1. Overview of MAUDE Database

The MAUDE database is maintained by the Office of Surveillance and Biometrics at FDA. This database contains adverse events and reportable product problems with medical devices. The database was fully implemented in August 1996, and contains Medical Device Reports (MDRs) submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems where devices are used in a “real world” setting, including:
 - rare, serious, or unexpected adverse events;
 - adverse events that occur during long-term device use;
 - adverse events associated with vulnerable populations; and
 - use error.

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an

event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Expanding upon these themes, the limitations therefore include:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Difficulty in confirming whether a device actually caused a specific event based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MAUDE data is subjected to reporting bias, attributable to potential causes such as reporting practices, increased media attention, and/or other agency regulatory actions.
- MAUDE data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

7.2. MAUDE Search Results: MMM Allograft Heart Valve Devices

The FDA conducted queries of the MAUDE database on December 2, 2013 to assess the number and types of reports for the one FDA-cleared MMM allograft heart valve, the SynerGraft Pulmonary Human Heart Valve (SG pulmonary valve), as well as the aortic version (SG aortic valve) which has not received clearance or approval. The search utilized the parameters of device product code, manufacturer name, brand name, and catalog number. There were no date restrictions included in the queries. The queries resulted in the identification of 28 MDRs on the SG pulmonary valves and 26 MDRs on the SG aortic valves.

The reported event types for the 28 SG pulmonary MDRs included death (4 MDRs), injury (17 MDRs), malfunction (1 MDR) and other (6 MDRs). The reported event types for the 26 SG aortic MDRs included injury (21 MDRs) and other (5 MDRs). There were no patient deaths reported for the SG aortic valves. Please refer to Appendix C for a complete listing of the reported SG valve MDRs.

For the SG pulmonary valves, Figure 1 displays the date, by year, when the MDRs were received by the FDA. The majority of reports were received after initial commercialization in 2000. Since the time of 510(k) clearance (2008), the number of reports has reduced to 2-3 MDRs per year.

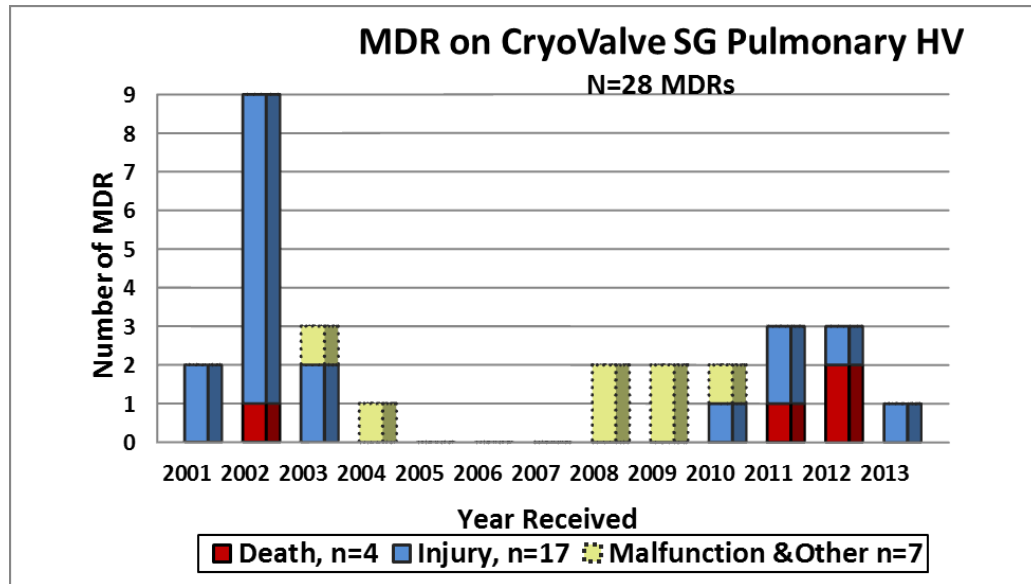


Figure 1: Year MDR received by FDA – SG Pulmonary Valves

For the SG pulmonary valves, the reported adverse events fall primarily into the following categories:

- Structural (n=16; includes the 4 death reports discussed below)
- Infection/endocarditis (n=5)
- Reaction/scarring (n=2)
- Mass (n=2)
- Incorrect size (n=2)
- Aneurysm (n=1)

For the SG aortic valves, Figure 2 displays the date, by year, when the MDRs were received by the FDA. During the period of 2002 to 2013, the number of annual reports was limited to 5 MDRs or fewer, with the exception of the 12 MDRs in 2011. The reason for the spike in MDRs in 2011 remains unclear.

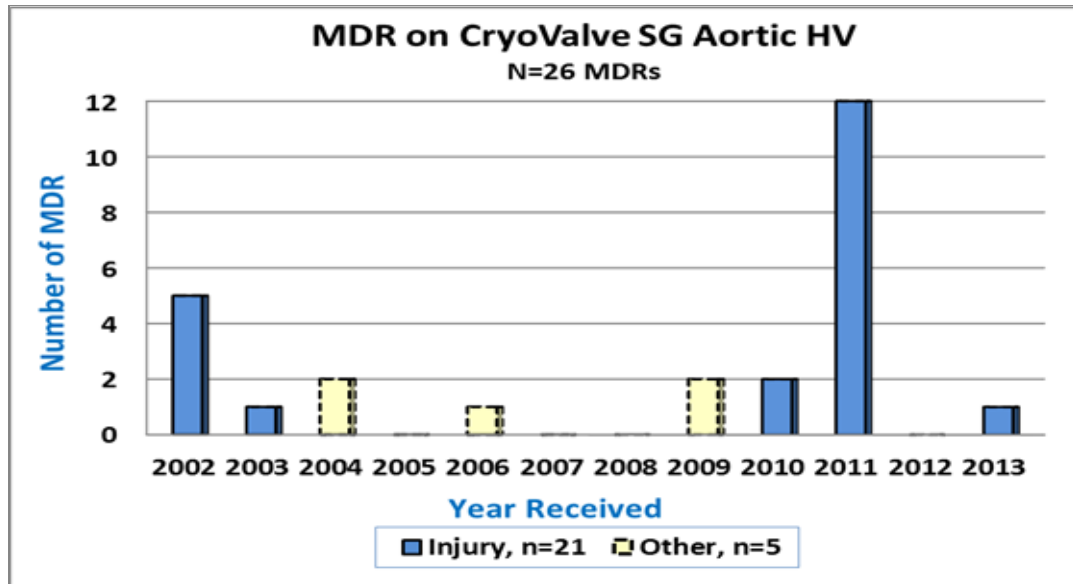


Figure 2: Year MDR received by FDA – SG Aortic Valves

For the SG aortic valves, the reported adverse events fall primarily into the following categories:

- Structural (n=24)
- Infection (n=1)
- Bleeding (n=1)

A discussion of the events and the timing of the occurrence of the events are presented for the SG pulmonary and SG aortic valves in the following sections.

7.2.1. Discussion of Events – SG Pulmonary Valves

The most frequently reported event was structural problems, including cuts, holes, tears, rips, cracks, delaminations, splits, incompetence, degradations, plaques, calcification of the device, valve stenosis or regurgitation/insufficiency. Of the 16 events where structural problems were reported, 10 (63%) were identified either after the thawing process and prior to device implant (2 MDRs), or within 24 hours post implant surgery (8 MDRs). Five of the remaining 6 events were identified within 6 months (3 MDRs) and between 6 months to 1 year (2 MDRs). The last event occurred at 11 years post implant (1 MDR). Fourteen of the 16 MDRs indicated that the patients required surgical interventions including valve explant (9 MDRs) and replacement of the stenotic/insufficient valve or repair with patch materials (4 MDRs) or Bioglue (1 MDR) for the tears/cracks in the valve. The remaining 2 MDRs of structural problems did not provide the information relevant to the interventions.

All 4 MDRs involving a patient death were associated with structural problems, including 3 reports which noted a similar bleeding/cardiac tamponade event secondary to the tears of the SG pulmonary valve where device structural

problems were observed on a 17 year-old male, shortly after implant. Further review of these reports revealed that the death reported in the 3 MDRs was most likely the same event which was reported from different reporting sources. Therefore, the death MDRs appear to have involved 2 actual patient deaths reported with the use of the device from 2000 through December 1, 2013. In the other death report, it is noted that the 45 year-old male patient presented with pulmonic stenosis and severe tricuspid regurgitation. The patient subsequently died approximately 2 months post-implant. The cause of death could not be obtained. Please refer to Appendix C for the details of the death MDRs.

Five infection/endocarditis injury events were reported. The implant dates and reported event dates were provided in 4 of the 5 MDRs. Using this information, the “time to event occurred” (TTEO) was calculated for these 4 events and determined as 6 months, 1 year, 5 years, and 7 years, respectively. The types of infectious micro-organisms reported in 4 MDRs included 2 cases of fungal and 2 cases of Staphylococcus infections. Two of the 5 infection cases required surgical explant of the HV and the other 3 cases involved antibiotic therapy.

Two MDRs noted “reaction/scarring” post implant of the SG pulmonary valve. One patient, a 37-year-old male, required an explant at 6 months post-implant due to “scarring and reaction.” The firm’s pathological testing noted “explanted pulmonary leaflet showing multiple calcification and degeneration of collagen and calcification with collagen degeneration and chronic inflammation for the explanted pulmonary artery.” Another patient, a 17-year-old male, developed a diastolic murmur and moderate to severe pulmonary insufficiency with no pulmonary stenosis 3 days post-implant. The surgeon suspected severe immunological reaction or technical failure of the replacement valve. The valve was explanted one week later. According to the manufacturer narrative of the MDR, a pathology report provided by the user facility stated that “Acellular pulmonary homograft with a minimal inflammatory infiltrate composed of T-lymphocytes and macrophages. The pathologist notes focal degenerative change in the valve leaflets However, the root cause of the graft failure is unknown.”

For the 2 mass events, the first mass event was identified by an echocardiogram 4 months post-implant. The 35-year-old male patient was initially treated with anticoagulation. At 9 months post-implant, the patient developed right ventricular dysfunction with Class II congestive heart failure. The patient required pulmonic valve dilation. No samples of the complaint valve were returned. No conclusion could be drawn as to a root cause for the reported event. The other event of mass formation was reported on a 33-year-old male who had a surgery to replace the valve due to “obstruction secondary to intra-homograft tumor mass” one year post-implant. The valve was explanted and analyzed. The explanting surgeon indicated that “There was no mass present within the lumen. There was an enfolding of the homograft valve which

involved the anterior wall of the homograft with what looked like significant inflammatory tissue.” A histology examination conducted by the firm indicated that the valve leaflets were intact and quite cellular. It appears that there may have been a folding of the valve conduit after implant, which became engulfed by scar tissue and, due to its location, may have exerted pressure on the valve conduit. The manufacturer reported no evidence of valve defect and stated that no conclusions could be drawn.

There were 2 reports of incorrect valve size. The valve was found to be smaller than documented in one report, and larger in the other report. It was reported that the surgery was prolonged due to the event. According to an analysis conducted by the manufacturer, as reported in one of the 2 reports, the actual size of the valve could not be verified since the valve was not returned. For the other report, no conclusions were provided due to limited information reported.

One MDR noted that during the implant of a SG pulmonary valve on a 4-month-old patient, a piece of native pericardium was utilized to complete the hood on the right ventricular outflow tract. The patient developed an aneurysm in the proximal portion of the outflow tract and required a surgical intervention 4 months post-implant. According to the manufacturer’s analysis, no conclusions could be drawn as to a possible relationship between the reported event and the valve, the procedure, or the use of pericardial tissue.

7.2.2. Discussion of Events – SG Aortic Valves

The most frequently reported event was structural problems (24 MDRs), including cuts, holes, tears, rips, cracks, splits, degradations, plaques, calcification of the device, valve stenosis or regurgitation/insufficiency. Of the 24 MDRs of structural problem(s), 23 contain “Time to Event” data. Four events (16%) of valve structural problem(s) were identified during implant surgery when SG aortic valve tear(s) were noted. The patients either required valve tissue repair with a patch or SG aortic valve explant. The remaining 19 events were identified within one year (2 MDRs), between 1 to 5 years (3 MDRs), or 5 to 10 years post implant (14 MDR). Most of the patients required surgical interventions including explant and replacement of the insufficient or stenotic/calcified valve (23 MDRs). The remaining one MDR noted that the patient required a patch for repairing a tear of the valve tissue at the distal suture line.

One report noted an infection of a 15-year-old female patient who developed a fever with drainage at the surgical wound site 2 weeks post implant. Sternal wound was positive for Staphylococcus Epidermidis. Although blood cultures were negative, the infection was treated as endocarditis, based on findings of transesophageal echocardiography and wound culture. According to the manufacturer analysis, per conversations with the surgeon, the delayed closure of the incision site likely contributed to the observed infection and the infection was not likely associated with the valve.

One report indicated that a 51-year-old patient had a bleeding from the non-coronary cusp/aortic mitral curtain area post implant when the patient was weaned from cardiopulmonary bypass pump. The patient was placed back on bypass pump twice and the SG aortic valve was replaced.

7.2.3. Time to Events after Implantation – SG Pulmonary Valves

The 28 MDRs were individually reviewed to categorize the reported problems. The “Time to Event Occurred” (TTEO) was calculated for the 28 MDRs, reflecting the time lapse between Implant Date and Event Date, where both data fields were reported or noted in the Event Text of the MDRs. The reported problems and TTEO calculations are provided in Table 2.

Table 2. Reported Problems and TTEO – SG Pulmonary Valves (28 MDRs)

Reported problem	Count	TTEO				
		<1 day	1 day - 6 mo	6 mo - 1 yr	>1 yr	Not Reported
*Structural Problems	16	10	3	2	1	0
**(Cardiac tamponade)	**(3)	**(3)	0	0	0	0
Infection/Endocarditis	5	0	1	1	2	1
Incorrect Size	2	2	0	0	0	0
Reaction/Scarring	2	0	2	0	0	0
Mass	2	0	1	1	0	0
Aneurysm	1	0	1	0	0	0

*Structural problems include cuts, holes, tears, rips, cracks, delaminations, splits, incompetent, degradations, plaques, or calcification of the device, or valve stenosis/regurgitation/insufficiency.

**The total number of the reported events is not equal to the number of the MDRs, as one report might indicate multiple events. For example, the 3 cardiac tamponade/bleeding events were reported secondary to the tears of the SG pulmonary heart valve where device structural problems were also reported.

7.2.4. Time to Events after Implantation – SG Aortic Valves

The 26 MDRs were individually reviewed to categorize the reported problems. The “Time to Event Occurred” (TTEO) was calculated for the 26 MDRs, reflecting the time lapse between Implant Date and Event Date, where both data fields were reported or noted in the Event Text of the MDRs. The reported problems and TTEO calculations are provided in Table 2.

Table 3. Reported Problems and TTEO – SG Aortic Valves (26 MDRs)

Reported problem	MDR Count	TTEO					
		<1 day	1 day - 1 mo	1 mo - 1 yr	1 - 5 yrs	5 - 10 yrs	Not Reported
Structural Problem	24	4	0	2	3	14	1
Infection	1	0	1	0	0	0	0
Bleeding	1	1	0	0	0	0	0

7.2.5. Summary of the MDR Review

The top reported device problem for the SG valves was structural problems. Two deaths (4 reports) associated with structural problems of the SG pulmonary valve were reported, including a death of a 17-year-old patient who developed cardiac tamponade/bleeding secondary to tears of the valve one hour post-implant. The other death report noted a 45 year-old male patient who presented with pulmonic stenosis and severe tricuspid regurgitation. The patient subsequently died approximately 2 months post-implant. The cause of death could not be obtained. The relationships between the “Reaction/scarring” and “Mass” events and the SG pulmonary valve remain unclear. This MAUDE search confirmed the life-supporting, life-sustaining nature of MMM allograft heart valves and that the risks to health of MMM allografts are consistent with other non-allograft replacement heart valves, all of which are regulated as Class III devices.

8. Summary

In light of the information available, the Panel will be asked to comment on whether MMM allograft heart valves meet the statutory definition associated with a Class III device designation, that is:

- insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, and
- the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury

as opposed to Class II, in which:

- general and special controls are sufficient to provide reasonable assurance of safety and effectiveness.

FDA proposes that MMM allograft heart valves meet the statutory definition of a Class III device because insufficient information exists to determine that general and special

controls are sufficient to provide reasonable assurance of their safety and effectiveness. Additionally, MMM allograft heart valves are life-supporting, life-sustaining devices.

If the Panel does not agree that MMM allograft heart valves meet the statutory definition of a Class III device, the Panel will be asked for input regarding whether the available scientific evidence supports a Class II determination with special controls, including which special controls could be established to mitigate the known risks to health associated with these devices. If the Panel supports classification into Class II, the Panel will further be asked to provide reasons for not recommending classification of the device into Class III.

For the purposes of classification, FDA considers the following items, among other relevant factors, as outlined in 21 CFR 860.7(b):

1. The persons for whose use the device is represented or intended;
2. The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;
3. The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and
4. The reliability of the device.

Part (g)(1) of this regulation further states that it “is the responsibility of each manufacturer and importer of a device to assure that adequate, valid scientific evidence exists, and to furnish such evidence to the Food and Drug Administration to provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use. The failure of a manufacturer or importer of a device to present to the Food and Drug Administration adequate, valid scientific evidence showing that there is reasonable assurance of the safety and effectiveness of the device, if regulated by general controls alone, or by general controls and performance standards, may support a determination that the device be classified into Class III.”

Note: Performance standards are an example of a type of special control.

8.1. Reasonable Assurance of Safety

According to 21 CFR 860.7(d)(1), “there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.”

FDA has identified potential risks to health associated with MMM allograft heart valves, based on literature and the currently reported adverse events. These include the following:

- Death
- Stroke
- Heart failure
- Myocardial infarction
- Hemorrhage
- Endocarditis
- Infection
- Cardiac arrhythmia
- Conduction system defect
- Valve stenosis
- Transvalvular regurgitation
- Perivalvular leak
- Structural valve deterioration
- Nonstructural dysfunction
- Hemolysis
- Valve thrombus
- Thromboembolism
- Renal insufficiency or failure
- Allosensitization, rejection, other immune responses
- Reoperation
- Explantation

The FDA will ask the Panel to comment on the risks to health identified and whether there are additional risks that should be considered for MMM allograft heart valves or if any of the identified risks should be removed. Additionally, the FDA will ask the Panel whether the evidence demonstrates a reasonable assurance of safety for the indications for use described above.

8.2. Reasonable Assurance of Effectiveness

According to 21 CFR 860.7(e)(1), “there is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.”

Given the limited availability of clinical data, as well as the limitations of those data (only 1 cleared MMM allograft heart valve, no randomized controlled studies, small patient numbers, etc.), it is challenging to draw conclusions regarding the effectiveness of MMM allograft heart valves, particularly regarding their long-term performance, immunogenicity, and potential for recellularization and/or host adaptation.

The FDA will ask the Panel whether there is a reasonable assurance of effectiveness for MMM allograft heart valves for the indications for use described above.

8.3. Overview of Proposed Classification

It is estimated that more than five million Americans are diagnosed with heart valve disease each year (Nkomo *et al.*, 2006). MMM allograft heart valves, one treatment option for heart valve disease, are life-supporting, life-sustaining devices with significant potential risks of illness or injury. A long history of clinical use of prosthetic heart valves has established numerous known risks to health, including death, valve thrombosis, thromboembolism (including stroke), myocardial infarction, cardiac arrhythmia, hemorrhage, endocarditis, valve stenosis, valve regurgitation, perivalvular leak, and others. Particular risks due to the nature of the MMM allograft valve and its processing include infection (non-sterile devices) and allosensitization. In addition, due to the novelty of MMM processing, isolated literature reports indicate the possibility for increased risks of structural valve deterioration, aneurismal degeneration (of conduit portion), thrombus, thromboembolism, stroke, and renal insufficiency or failure.

FDA believes that insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of MMM allograft heart valves. Only one MMM allograft heart valve has received clearance (K033484), and the voluntary post-clearance study (Clinical Trials identifier, NCT01092442) to collect long-term performance data is ongoing. While the literature has reported some prospective studies of the MMM allograft heart valve, there are no reports of randomized control clinical studies. Additionally, there are no well-established scientific methods to evaluate decellularization processes, to conduct *in vitro* evaluations (e.g., mechanical properties, durability), and/or to evaluate *in vivo* recellularization. New types of safety and effectiveness concerns are raised with each review of MMM allograft heart valves, including incomplete or variable decellularization (affecting antigenicity and calcification), limited *in vivo* recellularization (affecting valve structural integrity and dimensional stability), and extracellular matrix structural deterioration. Given the limited available information for these devices, FDA does not believe that special controls can be established to mitigate the known risks to health associated with these devices.

Due to the life-sustaining nature of MMM allograft heart valves as well as the potential impact of MMM processing on valve safety and effectiveness, and due to the novelty and potential variability of MMM processing (across manufacturers and over time), the Agency believes that the following are critical to ensuring the safety and effectiveness of MMM allograft heart valves:

- Premarket review of manufacturing information
- Pre-approval inspections
- Review of changes in manufacturing facility location where finished devices are manufactured

- Postmarket review of significant manufacturing changes to ensure that the changes are adequately evaluated and tested prior to implementation
- Annual reporting

The following table presents a summary of the regulatory requirements for three review paradigms: the current practice standard under 510(k); classification to class II, 510(k) with special controls; and classification to class III, PMA:

Table 4. Pre-Market and Post-Market Requirements for 510(k)s and PMAs

	Pre-Market Notification 510(k)	Pre-Market Notification 510(k) with Special Controls	Pre-Market Application PMA
Bench Testing	✓	✓	✓
Animal Studies	✓	✓	✓
Clinical Trials	510(k) integrity inspection only if FDA finds a “due cause”. Information kept on file by sponsor-open for inspection if product issue		PMA pivotal sites undergo BIMO inspections for integrity and assessment of sponsor quality/GCP over site
Premarket review of manufacturing			✓
Pre-approval inspection			✓
Review of any changes in manufacturing facilities			✓
Postmarket review of significant manufacturing changes			✓
Postmarket Surveillance	522 Postmarket Surveillance Studies	522 Postmarket Surveillance Studies	Post-Approval Studies
Annual Reporting			✓

This table clearly shows that the additional requirements recommended for improved pre- and post-market review of MMM allograft heart valves are already integrated in the PMA paradigm. FDA would have to create special controls under 510(k) to require the same level of regulatory control. Such special controls would be without precedent in many circumstances. As noted above, due to the criticality of the manufacturing process, the PMA process provides the most appropriate level of regulatory control for MMM allograft heart valves.

Based on the safety and effectiveness information gathered by the FDA, we recommend that MMM allograft heart valves, indicated for use in heart valve replacement procedures, be regulated as Class III devices. It is worth noting that all other replacement heart valves regulated within CDRH are regulated as Class III, PMA devices.

870.XXXX MMM allograft heart valve

- (a) *Identification.* A more-than-minimally manipulated (MMM) allograft heart valve is a human valve or valved-conduit that has been aseptically recovered from qualified donors, dissected free from the human heart, and then subjected to a manufacturing process (or processes) which alters the original relevant characteristics of the tissue (21 CFR 1271.3(f), 21 CFR 1271.10(a)(1), and 21 CFR 1271.20). The valve is then stored until needed by a recipient. The valve is intended to perform the function of any of the heart's natural valves.
- (b) *Classification.* Class III (premarket approval).

Based on the available scientific evidence, the FDA will ask the Panel for their recommendation on the appropriate classification of MMM allograft heart valves for use in heart valve replacement procedures.

9. References

- Bechtel JF, Gellissen J, et al. (2005). "Mid-term findings on echocardiography and computed tomography after RVOT-reconstruction: comparison of decellularized (SynerGraft) and conventional allografts." *European Journal of Cardio-Thoracic Surgery*. 27(3): 410-415; discussion 415.
- Bechtel JF, Muller-Steinhardt M, et al. (2003). "Evaluation of the decellularized pulmonary valve homograft (SynerGraft)." *Journal of Heart Valve Disease*. 12(6): 734-739; discussion 739-740.
- Bechtel JF, Stierle U, et al. (2008). "Fifty-two months' mean follow up of decellularized SynerGraft-treated pulmonary valve allografts." *Journal of Heart Valve Disease*. 17(1): 98-104; discussion 104.
- Bell P et al. (2003). Congenital abdominal aortic aneurysm: a case report. *Journal of Vascular Surgery*. 38(1): 190-193.
- Brown JW, Elkins RC, et al. (2010). "Performance of the CryoValve SG human decellularized pulmonary valve in 342 patients relative to the conventional CryoValve at a mean follow-up of four years." *Journal of Thoracic and Cardiovascular Surgery*. 139(2): 339-348.
- Brown JW, Ruzmetov M, et al. (2011). "Performance of SynerGraft decellularized pulmonary homograft in patients undergoing a Ross procedure." *Annals of Thoracic Surgery*. 91(2): 416-422; discussion 422-413.
- Burch PT, Kaza AK, et al. (2010). "Clinical Performance of Decellularized Cryopreserved Valved Allografts Compared With Standard Allografts in the Right Ventricular Outflow Tract." *Annals of Thoracic Surgery*. 90(4): 1301-1305.
- Clarke *et al.* (2001). Transformation of nonvascular acellular tissue matrices into durable vascular conduits. *Annals of Thoracic Surgery*. 71:5 SUPPL. (S433-S436)
- Dohmen PM, Lembcke A, et al. (2007). "Mid-term clinical results using a tissue-engineered pulmonary valve to reconstruct the right ventricular outflow tract during the ross procedure." *Annals of Thoracic Surgery*. 84(3): 729-736.
- Elkins RC, Lane MM, et al. (2001). "Humoral immune response to allograft valve tissue pretreated with an antigen reduction process." *Semin. Thorac. Cardiovasc. Surg.* 13(4 Suppl 1): 82-86.
- Garcia MM (1981). History and design of artificial heart valves. *Boletin de la Asociacion Medica de Puerto Rico*. 73(11): 567-573.

Hawkins JA, Hillman ND, et al. (2003). "Immunogenicity of decellularized cryopreserved allografts in pediatric cardiac surgery: comparison with standard cryopreserved allografts." *Journal of Thoracic and Cardiovascular Surgery*. 126(1): 247-252; discussion 252-243.

Hogan PG and O'Brien MF (2003). Improving the allograft valve: Does the immune response matter? *Journal of Thoracic and Cardiovascular Surgery*. 126: 1251-3.

Konuma TE, Devaney EJ, et al. (2009). "Performance of CryoValve SG decellularized pulmonary allografts compared with standard cryopreserved allografts." *Annals of Thoracic Surgery*. 88(3): 849-854; discussion 554-845.

Madden RL et al. (2005). A comparison of cryopreserved vein allografts and prosthetic grafts for hemodialysis access. *Annals of Vascular Surgery*. 19(5): 686-91.

Mitchell RN, Jonas RA, et al. (1995). "Structure-function correlations in cryopreserved allograft cardiac valves." *Annals of Thoracic Surgery*. 60(2 Suppl): S108-112; discussion S113.

Mitchell RN, Jonas RA, et al. (1998). "Pathology of explanted cryopreserved allograft heart valves: comparison with aortic valves from orthotopic heart transplants." *Journal of Thoracic and Cardiovascular Surgery*. 115(1): 118-127.

Neukamm CG, Dohlen G, et al. (2011). "Eight years of pulmonary valve replacement with a suggestion of a promising alternative." *Scandinavian Cardiovascular Journal*. 45(1): 41-47.

Nkomo V, Gardin M, Skelton T, et al. (2006). Burden of valvular heart diseases: a population-based study (part 2). *Lancet*. 1005-11.

Pompilio G, Polvani G, Piccolo G, Guarino A, Nocco A, Innocente A, et al. (2004). Six-year monitoring of the donor-specific immune response to cryopreserved aortic allograft valves: implications with valve dysfunction. *Annals of Thoracic Surgery*. 78: 557-63.

Ruzmetov M, Shah JJ, et al. (2012). "Decellularized versus standard cryopreserved valve allografts for right ventricular outflow tract reconstruction: a Literature Review on More than Minimally Manipulated (MMM) Allograft Heart Valves 16 single-institution comparison." *Journal of Thoracic and Cardiovascular Surgery*. 143(3): 543-549.

Schoen FJ, Mitchell RN, et al. (1995). "Pathological considerations in cryopreserved allograft heart valves." *Journal of Heart Valve Disease*. 4 Suppl 1: S72-75; discussion S75-76.

Sharp MA et al. (2004). A cautionary case: the SynerGraft vascular prosthesis. *European Journal of Vascular and Endovascular Surgery*. 27(1): 42-4.

Sievers HH, Stierle U, et al. (2003). "Decellularized pulmonary homograft (SynerGraft) for reconstruction of the right ventricular outflow tract: first clinical experience." *Zeitschrift für Kardiologie*. 92(1): 53-59.

Simon P et al. (2003). Early failure of the tissue engineered porcine heart valve SYNERGRAFT in pediatric patients. *European Journal of Cardio-Thoracic Surgery*. 23(6): 1002-6.

Stamm C et al. (2004). Biomatrix/polymer composite material for heart valve tissue engineering. *Annals of Thoracic Surgery*. 78(6): 2084-92.

Tavakkol Z, Gelehrter S, et al. (2005). "Superior durability of SynerGraft pulmonary allografts compared with standard cryopreserved allografts." *Annals of Thoracic Surgery*. 80(5): 1610-1614.

Vogt PR, Stallmach T, et al. (1999). "Explanted cryopreserved allografts: a morphological and immunohistochemical comparison between arterial allografts and allograft heart valves from infants and adults." *European Journal of Cardio-Thoracic Surgery*. 15(5): 639-644; discussion 644-635.

Yap CH, Skillington PD, et al. (2006). "Anti-HLA antibodies after cryopreserved allograft valve implantation does not predict valve dysfunction at three-year follow up." *Journal of Heart Valve Disease*. 15(4): 540-544.

Yap CH, Skillington PD, et al. (2008). "Human leukocyte antigen mismatch and other factors affecting cryopreserved allograft valve function." *Heart Surgery Forum*. 11(1): E42-45.

Zehr KJ, Yagubyan M, et al. (2005). "Aortic root replacement with a novel decellularized cryopreserved aortic homograft: postoperative immunoreactivity and early results." *Journal of Thoracic and Cardiovascular Surgery*. 130(4): 1010-1015.

Appendix A: Database Search Queries and Results – Search 1

Search 1 yielded 59 articles in Pubmed, 90 articles in Embase, and 86 articles in Web of Science.
Embase queries and results:

Session Results

Save | Delete | Print view | Export | Email | Combine using ☒ And ☐ Or Basic | Advanced Collapse

	Results
#3 'allograft heart valves' OR 'cryo valve' OR 'synergraft' AND [1990-2013]/py	90

Save | Delete | Print view | Export | Email Collapse

90 results for search #3 Search Details - Open

View | Print | Export | Email | Order | Add to Clipboard 1 - 25 next

Sort by: ☐ Relevance ☒ Publication Year ☐ Entry Date Selected: 0 (clear) or Select number of items

1 [Animal models for bench to bedside translation of regenerative cardiac constructs](#)
Quinn R.W.
[Article in Press] *Progress in Pediatric Cardiology* 2013

PubMed queries and results:

PubMed (((("allograft heart valves") OR "Cryo valve") OR "synergraft") AND (("1990/01/01"[PDat] : "2013/12/31"[PDat]

RSS Save search Advanced Search

Display Settings: ☒ Summary, 20 per page, Sorted by Recently Added Send to: ☒ Filters: [Manage Filters](#)

Results: 1 to 20 of 59 << First < Prev Page 1 of 3 Next > Last >>

☐ [Decellularized versus standard cryopreserved valve allografts for right ventricular outflow tract reconstruction: a single-institution comparison.](#)
1. Ruzmetov M, Shah JJ, Geiss DM, Fortuna RS.
J Thorac Cardiovasc Surg. 2012 Mar;143(3):543-9. doi: 10.1016/j.jtcvs.2011.12.032.
PMID: 22340029 [PubMed - indexed for MEDLINE]
[Related citations](#)

New feature
Try the new Display Set
Sort by Relevance

Find related data
Database: Select

Web of Science queries and results:

Web of Science®

Results Topic=("Allograft heart valves") OR Topic=(cryo valve) OR Topic=(synergraft)
Timespan=1900-2013. Databases=SCI-EXPANDED, SSCI.
Create Alert / RSS


Results: 86 Page 1 of 9 Go

Appendix B: Database Search Queries and Results – Search 2

Search 2 yielded 6 additional results in Pubmed, and no additional results in Embase or Web of Science.

PubMed

"homograft heart valve" NOT ("allograft heart valves" or "synergraft" or "cryograft")

 RSS [Save search](#) [Advanced](#)

[Display Settings:](#) ☒ Summary, 20 per page, Sorted by Recently Added

[Send to:](#) ☒ **Filter**

Results: 6

☐ [Cost-effectiveness of homograft heart valve replacement surgery: an introductory study.](#)

1. Yaghoubi M, Aghayan HR, Arjmand B, Emami-Razavi SH.
Cell Tissue Bank. 2011 May;12(2):153-8. doi: 10.1007/s10561-009-9165-9. Epub 2009 Dec 2.
PMID: 19949875 [PubMed - indexed for MEDLINE]
[Related citations](#)

☐ [\[Effects of cryopreservation on cellular viability and extracellular matrix of the aortic valves\].](#)

2. Lai Y, Zhang E, Lai D, Li Y, Xiao Z.
Sheng Wu Yi Xue Gong Cheng Xue Za Zhi. 2004 Dec;21(6):983-6. Chinese.
PMID: 15646347 [PubMed - indexed for MEDLINE]
[Related citations](#)

☐ [Identification of host and donor cells in porcine homograft heart valve explants by fluorescence in situ hybridization](#)

3.

Ne

Try

Sor

Titl

Hea

hon

Eva

val

Dec

allo

Appendix C: Public MAUDE Information on MMM Allograft Heart Valve Medical Device Reports (MDRs)

Appendix: Summary of 28 MDRs for CryoValve® SG Pulmonary Valve and Pulmonary Valve Conduit

Report Number	Event Type	Date Received	EVENT_TEXT
1063481-2012-00002, 1063481-2012-00003 and 3800070000-2011-0001 (3 reports on the same case)	DEATH	1/5/2012	ACCORDING TO THE REPORT, AN RV-PA CONDUIT PLACEMENT PROCEDURE WAS PERFORMED WITHOUT COMPLICATION. APPROXIMATELY ONE HOUR AFTER SURGERY THE PATIENT DISPLAYED SIGNS OF CARDIAC TAMPONADE. CPR WAS ADMINISTERED AND THE PATIENT WAS RETURNED TO SURGERY FOR CONTROL OF SUSPECTED BLEEDING. DURING SURGERY, A TEAR WAS FOUND IN THE PROXIMAL MUSCULAR PORTION OF THE CONDUIT OF THE ALLOGRAFT. THE PATIENT WAS PLACED ON CARDIOPULMONARY BYPASS AND THE SITE WAS REPAIRED WITH PATCH MATERIAL. HOWEVER, THE PATIENT DID NOT RECOVER.<End Text>
	DEATH	1/17/2012	ACCORDING TO THE REPORT, AN RV-PA CONDUIT PLACEMENT PROCEDURE WAS PERFORMED WITHOUT COMPLICATION. APPROXIMATELY ONE HOUR AFTER SURGERY THE PATIENT DISPLAYED SIGNS OF CARDIAC TAMPONADE. THE PATIENT WAS RETURNED TO SURGERY FOR CONTROL OF SUSPECTED BLEEDING. CPR WAS IN PROGRESS. THERE WAS A TEAR FOUND IN THE GRAFT. THE PATIENT WAS PLACED ON CARDIOPULMONARY BYPASS AND THE SITE WAS REPAIRED WITH PATCH MATERIAL. HOWEVER, THE PATIENT DID NOT RECOVER. THE TEAR WAS NOTED IN THE PROXIMAL MUSCULAR PORTION OF CONDUIT. THE HOSPITAL ALSO INDICATED THAT THE GRAFT APPEARANCE AND TEXTURE WERE THE SAME AS USUAL, OTHER THAN, A SLIGHT YELLOW COLOR.<End Text>
	DEATH	12/22/2011	ON 12/16/2011, THE PT UNDERWENT PLANNED PLACEMENT OF 25-MM PULMONARY VALVE CONDUIT (SYNERGRAFT) FOR THE RIGHT VENTRICLE TO THE PULMONARY ARTERY. INSP OF THE GRAFT PRIOR TO IMPLANTATION DID NOT INDICATE A TEAR. PT WAS SUCCESSFULLY WEANED FROM BYPASS AND TRANSFERRED TO PICU WHERE HE WOKE UP SHORTLY AFTER ARRIVAL. HE WAS EXTUBATED, AWAKE AND CONVERSING WITH NURSING STAFF. HE BECAME TACHYCARDIC AND SHIVERING. HE WAS GIVEN 25 MG OF DEMEROL AND APPROX FIVE MINUTES LATER HE BECAME HYPOTENSIVE, ARTERIAL LINE PRESSURE DROPPED AND CVP DROPPED TO APPROX ZERO. HE WAS REINTUBATED, RESUSCITATED WITH FLUIDS, BLOOD PRODUCT (ALBUMIN) AND MEDICATIONS (INCLUDING NARCAN). CHEST COMPRESSIONS WERE INITIATED THE TREATMENT TEAM LOST THE PULSE. HE WAS TAKEN BACK TO SURGERY FOR EMERGENT EXPLORATION AND REPAIR OF TEAR IN PULMONARY CONDUIT. INTRAOP FINDINGS INCLUDED A TEAR IN THE PULMONARY HOMOGRAFT CONDUIT NEAR THE PROXIMAL SUTURE LINE THROUGH THE FRIABLE MUSCLE COMPONENT OF THE CONDUIT. DURING SURGERY HIS PUPILS BECAME FIXED AND DILATED AND AN EEG SUGGESTED CORTICAL DEATH. HE HAD CONSIDERABLE BLEEDING AND PERIODS OF HYPOTENSION AFTER COMING OFF BYPASS. HE WAS MADE NO CODE AFTER DISCUSSION WITH THE FAMILY. A REPEAT EEG EARLY MORNING OF 12/17/2011 INDICATED THE PT WAS CLINICALLY DEAD. HE WAS EXTUBATED AT 1110 AND THERE WAS CARDIAC ASYSTOLE AT 1119. SEE SCANNED PAGE. <End Text>
1063481-2002-00028	DEATH	4/18/2002	IN 2002, THE CRYOPRESERVED PULMONARY VALVE AND CONDUIT WAS IMPLANTED INTO A PATIENT DURING A ROSS PROCEDURE. ACCORDING TO THE FOLLOWING MONTH'S OFFICE NOTE, THE PATIENT PRESENTED WITH PULMONIC STENOSIS STATUS-POST ROSS PROCEDURE. ECHOCARDIOGRAPHY STUDIES PERFORMED AT THE THAT TIME REPORTEDLY REVEALED MARKED DILATATION OF THE RIGHT VENTRICLE WITH EVIDENCE OF PULMONARY HYPERTENSION AND MODERATE TO SEVERE TRICUSPID REGURGITATION WITH A MEASURED GRADIENT OF 81 MMHG. ADDITIONALLY, THERE WAS EVIDENCE OF PULMONIC STENOSIS WITH AN INSTANTANEOUS GRADIENT OF 61 MMHG. APPROX 2 MONTHS POST-IMPLANT, THE PATIENT EXPIRED. TO DATE, NO DEFINITIVE CAUSE OF DEATH COULD BE OBTAINED.

Report Number	Event Type	Date Received	EVENT_TEXT
1063481-2001-00018	INJURY	9/21/2001	IN 2001, THE CRYOPRESERVED PULMONARY VALVE AND CONDUIT IN QUESTION WAS IMPLANTED INTO A PATIENT OF UNKNOWN MEDICAL HISTORY. ACCORDING TO THE OPERATING ROOM MATERIALS MANAGER AT THE SITE, THE VALVE POSSESSED LONGITUDINAL CUTS IN THE PULMONARY ARTERY UPON THAWING. THE SURGEON EXCISED THE AFFECTED PORTION OF THE VALVE PRIOR TO IMPLANTATION. UPON SEWING THE GRAFT IN PLACE, THE SURGEON NOTICED HOLES IN THE LEAFLETS. THE SURGEON REMOVED THE VALVE FROM THE PATIENT AND USED A FREESTYLE STENTLESS AORTIC VALVE IN THE PULMONARY VALVE POSITION.<End Text>
1063481-2001-00019	INJURY	10/19/2001	IN 2001, THE CRYOPRESERVED PULMONARY VALVE AND CONDUIT IN QUESTION WAS IMPLANTED INTO A PT DURING REPAIR OF TRUNCUS ARTERIOSUS. A PIECE OF NATIVE PERICARDIUM WAS UTILIZED TO COMPLETE THE HOOD ON THE RIGHT VENTRICULAR OUTFLOW TRACT. APPROXIMATELY FOUR MONTHS LATER, THE PT DEVELOPED AN ANEURYSM IN THE PROXIMAL PORTION OF THE OUTFLOW TRACT CAUSING INSUFFICIENCY, WHICH REQUIRED SURGICAL INTERVENTION. THE PULMONARY VALVE AND CONDUIT IN QUESTION WAS REMOVED IN 2001 AND AN 18 MM CRYOPRESEVED PULMONARY VALVE HOMOGRAFT WAS IMPLANTED.<End Text>
1063481-2002-00004	INJURY	1/8/2002	IN 2001, THE CRYOPRESERVED PULMONARY VALVE AND CONDUIT IN QUESTION WAS IMPLANTED INTO A PATIENT OF UNKNOWN MEDICAL HISTORY. ACCORDING TO THE REPORT, THE VALVE POSSESSED CUTS IN THE PULMONARY ARTERY UPON THAWING. THE SURGEON REPAIRED AND IMPLANTED THE HOMOGRAFT. AFTER IMPLANTATION, BLEEDING OCCURRED AT THE SITE OF THE CRACK, WHICH REQUIRED BYPASS, CROSS-CLAMP, AND BIOGLUE FOR REPAIR.<End Text>
1063481-2002-00013	INJURY	4/1/2002	IN 2000, THE CRYOPRESERVED PULMONARY VALVE AND CONDUIT IN QUESTION WAS IMPLANTED INTO A PATIENT DURING A ROSS PROCEDURE. THE PATIENT'S HISTORY WAS SIGNIFICANT FOR AORTIC INSUFFICIENCY, AORTIC STENOSIS, PREVIOUS AORTIC VALVE REPLACEMENT, AND MITRAL VALV REPLACEMENT DUE TO THEUMATIC HEART DISEASE. APPROXIMATELY ONE YEAR LATER, A MASS WAS DEMONSTRATED ON THE PULMONIC HOMOGRAFT DURING ROUTINE ECHOCARDIOGRAPHY, WHICH WAS PRODUCING OBSTRUCTION. ON THE NEXT DAY OF THE EVENT, THE PATIENT WAS RETURNED TO THE SURGICAL SUITE FOR REPLACEMENT OF THE HOMOGRAFT IN QUESTION DUE TO "OBSTRUCTION SECONDARY TO INTRAHOMOGRAFT TUMOR MASS". AT THAT TIME, ANOTHER CRYOPRESERVED PULMONARY VALVE AND CONDUIT WAS IMPLANTED.<End Text>
1063481-2002-00035	INJURY	7/25/2002	IN 2001, THE CRYOPRESERVED PULMONARY VALVE AND CONDUIT IN QUESTION WAS NOTED TO POSSESS A "RIP" IN THE CONDUIT. THE INVOLVED SURGEON UNSUCCESSFULLY ATTEMPTED TO REPAIR THE TISSUE. ACCORDING TO THE INITIAL INFO PROVIDED TO THE MANUFACTURER, THE TISSUE WAS NOT IMPLANTED AND NO PT CONTACT OR IMPACT WAS EXPERIENCED. ACCORDING TO NEW INFO PROVIDED TO THE MANUFACTURER, IN 2002 (VIA USER FACILITY MDR). THE DEVICE WAS IMPLANTED, BUT WAS SUBSEQUENTLY EXPLANTED DUE TO THE TISSUE DAMAGE. ANOTHER HOMOGRAFT WAS THAWED AND IMPLANTED.<End Text>
1063481-2002-00038	INJURY	8/26/2002	IN 2002, THE CRYOPRESERVED PULMONARY VALVE AND CONDUIT WAS IMPLANTED INTO A PT DURING A ROSS PROCEDURE. AT THAT TIME, THE PATIENT'S HISTORY WAS SIGNIFICANT FOR RHEUMATIC FEVER, ARRHYTHMIAS, AND PREVIOUS AORTIC VALVE REPLACEMENT. AT APPROXIMATELY SIX MONTHS POST-OPERATIVE, IT WAS REPORTED THAT THE RECIPIENT REQUIRED EXPLANT OF THE VALVE DUE TO "SCARRING AND REACTION".<End Text>
1063481-2002-00041	INJURY	8/29/2002	IN 2001, THE CRYOPRESERVED PULMONARY VALVE AND CONDUIT WAS IMPLANTED INTO A PATIENT WITH A KNOWN HISTORY OF BICUSPID VALVE LEFT VENTRICULAR HYPERTROPHY, AND MYXOMATOUS DEGENERATION. IN 2002, THE IMPLANTING SITE REPORTED THE PATIENT HAD BLOOD CULTURES INDICATING STAPHYLOCOCCUS EPIDERMIDIS. NO SOURCE OF INFECTION WAS NOTED. ACCORDING TO THE REPORT, THE PATIENT DEVELOPED A MEDIASTINAL ABSCESS, WHICH ERODED THE PULMONARY ARTERY AND AORTA. THE VALVE WAS EXPLANTED (APPROXIMATELY 6 MONTHS POST-IMPLANT).<End Text>

Report Number	Event Type	Date Received	EVENT_TEXT
1063481-2002-00044	INJURY	8/29/2002	IN 2001, THE CRYOPRESERVED PULMONARY VALVE AND CONDUIT WAS IMPLANTED INTO A PATIENT WITH A HISTORY OF BICUSPID VALVE, LEFT VENTRICULAR HYPERTROPHY, AND PATENT FORAMEN OVALE. CONCOMITANTLY, THE PATIENT UNDERWENT REPLACEMENT OF THE ASCENDING AORTA WITH A DACRON GRAFT. PER REPORTS RECEIVED IN JULY, 2002, APPROXIMATELY 4 MONTHS POST-OP AN ECHOCARDIOGRAM INDICATED TWO HIGHLY MOBILE ATTACHED ECHODENSE MASSES ON THE GRAFT. THE PATIENT SUBSEQUENTLY WAS TREATED WITH ANTICOAGULATION THERAPY. AT APPROXIMATELY 9 MONTHS POST-IMPLANT, THE PATIENT DEVELOPED RIGHT VENTRICULAR DYSFUNCTION WITH CLASS II CONGESTIVE HEART FAILURE SYMPTOMS REQUIRING PULMONIC HOMOGRAFT DILATION.<End Text>
1063481-2002-00049	INJURY	10/3/2002	IN 2001, THE CRYOPRESERVED PULMONARY VALVE AND CONDUIT WAS IMPLANTED INTO THE AORTIC POSITION OF A PT HAVING A HISTORY OF AORTIC STENOSIS, ASCENDING AORTIC ANEURYSM, AND CORONARY ARTERY DISEASE. CONCOMITANTLY, THE AORTIC ANEURYSM WAS REPAIRED WITH A SYNTHETIC GRAFT, WHILE THE CORONARY ARTERIES WERE BYPASSED USING THE PATIENT'S MAMMARY ARTERY AND SAPHENOUS VEIN. IN 2002, THE PATIENT UNDERWENT SURGERY TO REPLACE THE SYNTHETIC GRAFT, WHICH WAS REPORTED TO BE INFECTED AND ANEURYSMAL. AT THAT TIME, A TISSUE BIOPSY OF THE PULMONARY VALVE AND CONDUIT WAS OBTAINED AND REVEALED THE PRESENCE OF CANDIDA. THE PATIENT WAS REPORTEDLY TREATED WITH ANTI-FUNGAL THERAPY, AND THE PULMONARY VALVE AND CONDUIT REMAINS IMPLANTED.<End Text>
1063481-2002-00055	INJURY	12/2/2002	IN 2001, THE CRYOPRESERVED PULMONARY VALVE AND CONDUIT WAS IMPLANTED INTO A PATIENT WITH A HISTORY OF TETRALOGY OF FALLOT (PREVIOUSLY REPAIRED IN 1999) AND SEVERE PULMONARY INSUFFICIENCY. THE SURGEON REPORTED THAT APPROXIMATELY ONE YEAR AFTER IMPLANT, THE PULMONARY VALVE WAS EXPLANTED DUE TO SEVERE PULMONARY INSUFFICIENCY. ADDITIONAL INFORMATION CONCERNING THIS INCIDENT HAS BEEN REQUESTED.<End Text>
1063481-2003-00067	INJURY	3/31/2003	THE CRYOPRESERVED PULMONARY VALVE AND CONDUIT WAS IMPLANTED INTO A PT DURING A SURGICAL PROCEDURE OF UNKNOWN TYPE. THE PT'S MEDICAL HISTORY IS UNKNOWN. REPORTEDLY, THE PT DEVELOPED A POSTOPERATIVE INFECTION ASSOCIATED WITH THE ORGANISM COAGULASE NEGATIVE, STAPHYLOCOCCUS (SPECIES UNKNOWN). REPORTEDLY, THE PT WAS TREATED WITH IV ANTIBIOTICS AND RELEASED TO HOME HEALTHCARE. NO ADD'L INFO HAS BEEN PROVIDED.<End Text>
1063481-2003-00073	INJURY	5/28/2003	IN 2003, THE CRYOPRESERVED PULMONARY VALVE AND CONDUIT WAS IN THE PROCESS OF BEING IMPLANTED INTO A PT OF UNREPORTED MEDICAL HISTORY. DURING THE PROCEDURE, THE IMPLANTING SURGEON REPORTEDLY OBSERVED A TEAR ON A LEAFLET AND "VERY FRIABLE" TISSUE IN THE SURROUNDING AREA. ACCORDING TO THE SURGEON'S REPORT, ATTEMPTS TO REPAIR THE VALVE WERE UNSUCCESSFUL. SUBSEQUENTLY, THE VALVE WAS EXPLANTED AND REPLACED WITH A MOSAIC VALVE (MFR UNKNOWN).<End Text>
1063481-2010-00035	INJURY	9/16/2010	APPROXIMATELY SEVEN YEARS AFTER IMPLANT OF THE HEART VALVE, A FUNGAL VEGETATION REPORTEDLY DEVELOPED IN THE CONDUIT. HOWEVER, THE SURGEON DOES NOT BELIEVE THE ORGANISM WAS INTRODUCED BY THE ALLOGRAFT OR AT THE TIME OF IMPLANT.<End Text>
1063481-2011-00006	INJURY	2/10/2011	ACCORDING TO THE REPORT, DURING UNRELATED CARDIAC OPERATION THE SURGEON NOTICED THE PULMONARY VALVE & CONDUIT SG ALLOGRAFT HAD STENOSIS AND NEEDED TO BE EXPLANTED.<End Text>
1063481-2011-00048	INJURY	9/12/2011	ACCORDING TO THE REPORT, THE ALLOGRAFT WAS EXPLANTED APPROXIMATELY 11 YEARS AFTER IMPLANT DUE TO CALCIFICATION AND STENOSIS.<End Text>
1063481-2011-00054	INJURY	1/3/2012	ACCORDING TO THE REPORT, THE ALLOGRAFT WAS IMPLANTED IN 2002 AS PART OF A ROSS PROCEDURE. APPROXIMATELY FIVE YEARS AFTER IMPLANT, THE PATIENT PRESENTED SEPTIC. THE PULMONARY ALLOGRAFT VALVE WAS FOUND TO HAVE VEGETATION AND ENDOCARDITIS WAS DIAGNOSED. THE PATIENT WAS HOSPITALIZED AND TREATED WITH IV ANTIBIOTICS.<End Text>

Report Number	Event Type	Date Received	EVENT_TEXT
1063481-2013-00032	INJURY	8/26/2013	ACCORDING TO THE REPORT, THE SYNERGRAFT PULMONARY VALVE AND CONDUIT WAS LISTED AS 14MM. HOWEVER, WHEN THE SURGEON MEASURED THE GRAFT WITH A HEGAR DIALATOR, HE MEASURED IT TO THE 16MM, BUT BELIEVES IT MAY HAVE BEEN CLOSER TO 18MM. THIS MADE THE CASE MORE DIFFICULT FROM THE STANDPOINT OF FITTING IT IN THE CHEST AND ATTACHING THE GRAFT TO MUCH SMALLER PULMONARY ARTERIES. THE SURGERY WAS PROLONGED DUE TO THIS.<End Text>.
1063481-2004-00037	Malfunction	10/13/2004	A PT WITH SIGNIFICANT HISTORY OF ATRIAL SEPTAL DEFECT (ASD) PULMONARY VALVE STENOSIS, ASD CLOSURE AND PULMONARY VALVECTOMY (1996), AND PULMONARY INSUFFICIENCY WITH DILATED RIGHT VENTRICLE PREOPERATIVE ECHOCARDIOGRAM DEMONSTRATED WIDE OPEN PULMONARY REGURGITATION AND MILD TRICUSPID REGURGITATION. THE HOMOGRAFT WAS SUBSEQUENTLY IMPLANTED IN 2003 WITHOUT COMPLICATION. THE PT'S INITIAL POSTOPERATIVE COURSE WAS UNEVENTFUL. HOWEVER, AT APPROXIMATELY THREE DAYS AFTER SURGERY THE PT DEVELOPED A DIASTOLIC MUMUR AND ECHOCARDIOGRAM DEMONSTRATED MODERATE TO SEVERE PULMONARY INSUFFICIENCY WITH NO PULMONARY VALVE STENOSIS. THE SURGEON SUSPECTED SEVERE IMMUNOLOGICAL REACTION OR TECHNICAL FAILURE OF THE REPLACEMENT VALVE AND REPEATED SURGERY WITH EXPLANT OF THE HOMOGRAFT WAS PERFORMED ONE WEEK LATER. THE VALVE WAS REPLACED WITH A 26MM HANCOCK CONDUIT AND NO ADDITIONAL COMPLICATIONS HAVE BEEN REPORTED.<End Text> ATRIAL SEPTAL DEFECT (ASD), PULMONARY VALVE STENOSIS, ASD CLOSURE AND PULMONARY VALVECTOMY (APRIL 21, 1986), AND PULMONARY INSUFFICIENCY WITH DILATED RIGHT VENTRICLE.<End Text>
1063481-2008-00015	OTHER	5/9/2008	THE ALLOGRAFT WAS NOTED TO BE CRACKED AT IMPLANT. HOWEVER, THEY IMPLANTED IT ANYWAY AND IT "FELL APART".<End Text>
1063481-2008-00019	OTHER	7/14/2008	ACCORDING TO THE REPORT, THE ALLOGRAFT WAS THAWED AND THE SURGEON NOTED THAT IT WAS SMALLER THAN THE LABELED DIMENSIONS. <End Text>
1063481-2009-00003	OTHER	2/26/2009	ACCORDING TO THE REPORT, THE VALVE WAS IMPLANTED DURING A ROSS PROCEDURE PERFORMED IN MAY, 2008 AND WAS "GOOD LOOKING" APPROX ONE MONTH AFTER IMPLANT. APPROX SIX MONTHS AFTER IMPLANT, THE VALVE DEVELOPED "SEVERE STENOSIS AND DEGENERATION".<End Text>
1063481-2009-00028	OTHER	12/15/2009	ACCORDING TO THE REPORT, WHILE THE SYNERGRAFT PULMONARY VALVE AND CONDUIT WAS BEING IMPLANTED ONE OF THE VALVE LEAFLETS PROLAPSED BUT WAS REPAIRED. THE ALLOGRAFT REMAINS IMPLANTED.<End Text>
1063481-2010-00010	OTHER	4/16/2010	ACCORDING TO THE REPORT, THE SYNERGRAFT PULMONARY VALVE AND CONDUIT WAS EXPLANTED ONE YEAR POST-OPERATIVELY DUE TO PULMONARY INSUFFICIENCY.<End Text>
1063481-2003-00077	OTHER	7/16/2003	IN 2003 A PT OF UNKNOWN MEDICAL HISTORY UNDERWENT PULMONARY VALVE REPLACEMENT (PROCEDURE UNSPECIFIED) WITH A CRYOPRESERVED PULMONARY VALVE AND CONDUIT SG. ACCORDING TO THE SURGEON'S INCIDENT REPORT TO THE MFR, AT APPROX 1 HOUR INTO THE PROCEDURE THE VALVE WAS EXPLANTED SECONDARY TO UNSATISFACTORY TISSUE QUALITY. SPECIFICALLY, THE SURGEON DESCRIBED THE VALVE TISSUE AS FRIABLE AND REPORTED THAT THE ALLOGRAFT POSSESSED A TEAR IN THE INTIMAL LAYER OF THE CONDUIT NEAR THE SINUS. ACCORDING TO IMPLANT RECORDS, THE PT WAS PLACED BACK ON BYPASS AND A SECOND CRYOPRESERVED PULMONARY VALVE AND CONDUIT SG WAS THAWED AND IMPLANTED WITH NO FURTHER COMPLICATIONS REPORTED TO DATE.<End Text>

Appendix: Summary of 26 MDRs for CryoValve® SG Aortic Human Heart Valve

Report Number	Event Type	Date Received	EVENT_TEXT
1063481-2002-00011	INJURY	3/20/2002	IN 2000, THE CRYOPRESERVED AORTIC VALVE AND CONDUIT IN QUESTION WAS IMPLANTED INTO A PATIENT DURING AN RVOT RECONSTRUCTION. AT THAT TIME, THE PT'S HISTORY WAS SIGNIFICANT FOR PULMONARY REGURGITATION/INSUFFICIENCY, STENOSIS, CONGESTIVE HEART FAILURE, AND TETRALOGY OF FALLOT. AT APPROXIMATELY THREE MONTHS POST-OP (2001), THE PATIENT PRESENTED WITH MODERATE PULMONARY REGURGITATION/INSUFFICIENCY. SIX AND HALF MONTHS LATER, THE PATIENT UNDERWENT REPEAT RVOT WITH USE OF A CRYOPRESERVED PULMONARY VALVE AND TRICUSPID VALVE ANNULOPLASTY DUE TO SEVERE PULMONARY INSUFFICIENCY AND SEVERE TRICUSPID REGURGITATION.<End Text>
1063481-2002-00037	INJURY	8/8/2002	ON 7/2002, THE CRYOPRESERVED AORTIC VALVE AND CONDUIT IN QUESTION WAS THAWED AND IMPLANTED INTO A PATIENT OF UNKNOWN MEDICAL HISTORY. ACCORDING TO THE SURGEON'S REPORT, UPON IMPLANTATION THE CONDUIT TISSUE TORE AT THE DISTAL SUTURE LINE (ON THE VALVE SIDE). REPORTEDLY, THE TEAR ENLARGED RESULTING IN BLEEDING AND REQUIRING A PATCH.<End Text>
1063481-2002-00050	INJURY	11/1/2002	ACCORDING TO PT'S MEDWATCH REPORT: "AS ONE WHO RECEIVED A HIGHLY DEFECTIVE HOMOGRAFT FROM CRYOLIFE-IT RIPPED DURING SURGERY, MEANING PT WAS ON A HEART-LUNG MACHINE FOR 10 HOURS AND IN SURGERY FOR 14 HOURS WHILE THEY PUT IN ANOTHER VALVE-PT IS GREATLY CONCERNED WITH CRYOLIFE'S QUALITY CONTROL PROGRAM. PT'S SURGERY WAS PERFORMED BY DR. GIVEN THAT PT NEARLY DIED DURING SURGERY. PT WOULD BE HAPPY TO DISCUSS THEIR CASE WITH THE FDA RELATING TO ITS CURRENT INVESTIGATION OF CRYOLIFE." THE IMPLANTING SURGEON STATED THAT THE PT PRESENTED WITH SEVERE CALCIFICATION OF TISSUE, WHICH REQUIRED EXTENSIVE DEBRIDEMENT PRIOR TO IMPLANTATION OF THE COMPLAINT VALVE. THE SURGEON ATTRIBUTED THE AE TO THE DIFFICULT PT ANATOMY, AND HE COULD NOT DETERMINE THE CAUSE OF THE CRYOVALVE TEAR, WHICH WAS NOT IDENTIFIED PRIOR TO IMPLANT. THE COMPLAINT VALVE WAS EXPLANTED AND REPLACED WITH A SECOND CRYOVALVE. THE PT IS REPORTEDLY DOING WELL.<End Text> SEVERE CALCIFICATION OF PT'S NATIVE AORTIC VALVE.<End Text>
1063481-2002-00051	INJURY	11/8/2002	IN 2002, THE CRYOPRESERVED AORTIC VALVE AND CONDUIT WAS IMPLANTED INTO THE AORTIC POSITION OF A PT HAVING A HISTORY OF SUBAORTIC STENOSIS, PULMONARY STENOSIS, AORTIC VALVE REPLACEMENT TIMES 3, AND NONCOMPLIANCE WITH ANTICOAGULANT MEDICATIONS. THE SURGICAL PROCEDURE WAS COMPLICATED BY DIFFUSE BLEEDING, AND THE PT'S CHEST WAS LEFT OPEN WITH PACKING UNTIL THE DAY AFTER SURGERY. APPROX 2 WEEKS AFTER SURGERY, THE PT DEVELOPED A FEVER WITH DRAINAGE AT THE WOUND SITE. STERNAL WOUND WAS POSITIVE FOR STAPHYLOCOCCUS "EPIDERMIDIS". ALTHOUGH BLOOD CULTURES WERE NEGATIVE, OBSERVED INFECTION WAS TREATED AS ENDOCARDITIS, BASED ON FINDINGS OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY AND WOUND CULTURE.<End Text>
1063481-2003-00063	INJURY	2/7/2003	IN 2003, THE CRYOPRESERVED AORTIC VALVE AND CONDUIT WAS IMPLANTED INTO A PT WITH UNKNOWN MEDICAL HISTORY. DURING IMPLANTATION, REPORTEDLY THE VALVE TORE AWAY FROM THE HEART MUSCLE REQUIRING REMOVAL OF THE VALVE. REPEATED ATTEMPTS TO OBTAIN ADDITIONAL DETAILS ABOUT THIS EVENT HAVE NOT PRODUCED ADDITIONAL INFORMATION.<End Text>
1063481-2004-00008	Injury	4/14/2004	DURING IMPLANTATION OF A CRYOPESERVED AORTIC VALVE AND CONDUIT-SG INTO A PATIENT IN 2004. IT WAS REPORTED THAT SUTURES (USED BY THE SURGEON DURING IMPLANTATION) PULLED THROUGH THE HOMOGRAFT CAUSING TEARS. DUE TO UNREPAIRABLE TEARS, THE HOMOGRAFT WAS SUBSEQUENTLY REMOVED FROM THE PATIENT AND ANOTHER VALVE WAS IMPLANTED WITH NO FURTHER COMPLICATIONS REPORTED TO THE MFR.<End Text>

Report Number	Event Type	Date Received	EVENT_TEXT
1063481-2004-00012	Injury	5/12/2004	IN 2001, THE CRYOPRESERVED AORTIC VALVE AND CONDUIT REFERENCED IN THE REPORT WAS PLACED INTO A PT OF UNK MEDICAL HISTORY. ACCORDING TO INFO PROVIDED BY THE SURGEON, THE PT DEVELOPED FATIGUE WITH EXERCISE OVER THE LAST YEAR (PREVIOUS TO EXPLANTATION) 3 yrs post-op. IT WAS INDICATED THAT THE PT HAD PROGRESSIVE DEVELOPMENT OF HOMOGRAFT STENOSIS AT THE LEVEL OF THE VALVE LEAFLETS WITH DENSE CALCIFICATION ON ECHOCARDIOGRAM. CT SCAN ALSO REVEALED SIGNIFICANT CALCIUM DEPOSITION IN THE HOMOGRAFT MUSCLE CUFF AND AORTIC WALL. REPORTEDLY, THE FINDINGS AT SURGERY WERE CONSISTENT WITH THE PRE-OPERATIVE STUDIES. THE VALVE WAS SUBSEQUENTLY REMOVED FROM THE PT (SPECIFIC DATE UNK).<End Text>
1063481-2006-00034	Injury	8/26/2006	THE SYNERGRAFT AORTIC VALVE AND CONDUIT ALLOGRAFT WAS IMPLANTED IN 2003 INTO A PATIENT WITH A HISTORY OF SEVERE AORTIC STENOSIS, OBESITY, AND POSSIBLE ENDOCARDITIS. NO COMPLICATIONS WERE REPORTED TO CRYOLIFE IMMEDIATELY AFTER THE ALLOGRAFT WAS IMPLANTED. HOWEVER, 3 MOS LATER THE PATIENT UNDERWENT REOPERATION FOR REMOVAL OF THE ALLOGRAFT DUE TO SEVERE AORTIC INSUFFICIENCY.<End Text>
1063481-2009-00006	Injury	4/10/2009	THE SYNERGRAFT AORTIC VALVE WAS IMPLANTED ON 09/16/2003 AND WAS EXPLANTED ON 04/02/2009 DUE TO AORTIC STENOSIS.<End Text>
1063481-2009-00020	Injury	8/4/2009	ACCORDING TO THE REPORT, A SYNERGRAFT AORTIC VALVE AND CONDUIT WAS EXPLANTED 5.7 YEARS AFTER IMPLANT. THE REASON FOR EXPLANTATION IS CURRENTLY UNK. HOWEVER, UPON EXPLANT, IT WAS DISCOVERED THAT THE ALLOGRAFT WAS CALCIFIED. <End Text>
1063481-2010-00016	INJURY	8/9/2010	DURING A RETROSPECTIVE CLINICAL STUDY, IT WAS NOTED THAT SYNERGRAFT AORTIC VALVE AND CONDUIT WAS IMPLANTED IN A RIGHT VENTRICULAR OUTFLOW TRACT (RVOT) RECONSTRUCTION AND EXTRACARDIAC RA-PA CONDUIT PLACEMENT PROCEDURE TO REPLACE A PULMONARY VALVE AND CONDUIT ALLOGRAFT DUE TO SEVERE TRICUSPID REGURGITATION. APPROXIMATELY TWO YEARS AFTER IMPLANT THE PT DEVELOPED MILD PULMONARY REGURGITATION/INSUFFICIENCY. THEN APPROXIMATELY 6.5 YEARS AFTER THE IMPLANT OF THE SYNERGRAFT ALLOGRAFT IT WAS EXPLANTED DUE TO SEVERE STENOSIS (90 MMHG GRADIENT) AND MILD REGURGITATION. <End Text>
1063481-2010-00017	INJURY	7/7/2010	DURING A RETROSPECTIVE CLINICAL STUDY, IT WAS NOTED THAT SYNERGRAFT AORTIC VALVE AND CONDUIT WAS IMPLANTED IN A RIGHT VENTRICULAR OUTFLOW TRACT (RVOT) RECONSTRUCTION PROCEDURE TO REPLACE A PREVIOUSLY IMPLANTED CRYOVALVE ALLOGRAFT THAT WAS SAID TO HAVE FAILED DUE TO INSUFFICIENCY. APPROXIMATELY FIVE YEARS AFTER THE IMPLANT OF THE SYNERGRAFT ALLOGRAFT THE PATIENT DEVELOPED MILD PULMONARY REGURGITATION/INSUFFICIENCY. THREE MONTHS AFTER THIS DIAGNOSIS THE ALLOGRAFT STENOSED AND BALLOON DILATATION WAS NECESSARY. APPROXIMATELY SEVEN YEARS AFTER IMPLANTING THE SYNERGRAFT AORTIC VALVE AND CONDUIT WAS EXPLANTED DUE TO CALCIFICATION AND STENOSIS. <End Text>
1063481-2011-00010	INJURY	3/10/2011	AS PART OF THE CRYOVALVE SG AORTIC HUMAN HEART VALVE RETROSPECTIVE/PROSPECTIVE, MULTI-CENTER COHORT STUDY, AN EXPLANT FORM INDICATEING THE FOLLOWING EVENT WAS RECIEVED. ACCORDING TO THE REPORT, 4.6 YEARS AFTER IMPLANT OF THE SYNERGRAFT AORTIC VALVE & CONDUIT ALLOGRAFT THE ALLOGRAFT WAS EXPLANTED DUE TO STRUCTURAL DETERIORATION, CALCIFICATION, AND INSUFFICIENCY, STENOSIS OR OBSTRUCTION OF THE ALLOGRAFT CONDUIT, AND STENOSIS OR OBSTRUCTION OF THE VALVE. THE OPERATIVE NOTES INDICATE THERE WAS MODERATELY SEVERE AORTIC ALLOGRAFT INSUFFICIENCY WITH MODERATE AORTIC STENOSIS.<End Text>

Report Number	Event Type	Date Received	EVENT_TEXT
1063481-2011-00013	INJURY	3/10/2011	AS PART OF THE CRYOVALVE SG AORTIC HUMAN HEART VALVE RETROSPECTIVE/PROSPECTIVE, MULTI-CENTER, COHORT STUDY (SGA0903.000), AN EXPLANT FORM INDICATING THE FOLLOWING EVENT WAS RECEIVED. ON 2/3/2010, THE PATIENT UNDERWENT AN EXPLANT PROCEDURE FOR THE FOLLOWING: UNACCEPTABLE HEMODYNAMICS; ALONG WITH CALCIFICATION, VALVE LEAFLET DEGENERATION, INSUFFICIENCY, AND PERIVALVULAR LEAK. THE NATURE OF THE EVENT WAS SEVERE AORTIC VALVE REGURGITATION AND EVIDENCE OF LEFT VENTRICULAR ENLARGEMENT, EJECTION FRACTION 67%. THE ALLOGRAFT WAS EXPLANTED. THE SURGEON IS OVERALL SATISFIED WITH THE PERFORMANCE OF THE ALLOGRAFT AND STATED THE PATIENTS HAD JUST OUTGROWN THE VALVES.<End Text>
1063481-2011-00014	INJURY	3/10/2011	AS PART OF THE CRYOVALVE SG AORTIC HUMAN HEART VALVE RETROSPECTIVE/PROSPECTIVE, MULTI-CENTER, COHORT STUDY (SGA0903.000), AN EXPLANT FORM INDICATING THE FOLLOWING EVENT WAS RECEIVED. ON 6/30/2008, THE PATIENT UNDERWENT AN EXPLANT PROCEDURE FOR THE FOLLOWING: UNACCEPTABLE HEMODYNAMICS; ALONG WITH CALCIFICATION AND INSUFFICIENCY. THE NATURE OF THE EVENT WAS EJECTION FRACTION OF 35%, SEVERE AORTIC HOMOGRFT VALVE DISFUNCTION AND MODERATE TO SEVERE MITRAL VALVE REGURGITATION. THE ALLOGRAFT WAS EXPLANTED. THE SURGEON IS OVERALL SATISFIED WITH THE PERFORMANCE OF THE ALLOGRAFT AND STATED THE PATIENTS HAD JUST OUTGROWN THE VALVES.<End Text>
1063481-2011-00015	INJURY	3/10/2011	AS PART OF THE CRYOVALVE SG AORTIC HUMAN HEART VALVE RETROSPECTIVE/PROSPECTIVE, MULTI-CENTER, COHORT STUDY (SGA0903.000), AN EXPLANT FORM INDICATING THE FOLLOWING EVENT WAS RECEIVED. ON 12/3/2009, THE PATIENT UNDERWENT AN EXPLANT PROCEDURE FOR THE FOLLOWING: UNACCEPTABLE HEMODYNAMICS; ALONG WITH VALVE LEAFLET DEGENERATION AND INSUFFICIENCY. THE NATURE OF THE EVENT WAS MODERATE-SEVERE AORTIC PROSTHETIC REGURGITATION, THICKENED LEAFLETS, TRICUSPID PROLAPSE AND SEPTAL DEFECT, RIGHT AND LEFT ATRIAL ENLARGEMENT. THE ALLOGRAFT WAS EXPLANTED. THE SURGEON IS OVERALL SATISFIED WITH THE PERFORMANCE OF THE ALLOGRAFT AND STATED THE PATIENTS HAD JUST OUTGROWN THE VALVES.<End Text>
1063481-2011-00016	INJURY	3/10/2011	AS PART OF THE CRYOVALVE SG AORTIC HUMAN HEART VALVE RETROSPECTIVE/PROSPECTIVE, MULTI-CENTER, COHORT STUDY (SGA0903.000), AN EXPLANT FORM INDICATING THE FOLLOWING EVENT WAS RECEIVED. ON 9/29/2008, THE PATIENT UNDERWENT AN EXPLANT PROCEDURE FOR THE FOLLOWING: UNACCEPTABLE HEMODYNAMICS; ALONG WITH INSUFFICIENCY AND STENOSIS OR OBSTRUCTION OF VALVE.AS PART OF THE CRYOVALVE SG<End Text>
1063481-2011-00029	INJURY	5/25/2011	INFORMATION REGARDING THE EXPLANT OF A SYNERGRAFT AORTIC VALVE AND CONDUIT ALLOGRAFT WAS OBTAINED THROUGH A RETROSPECTIVE CLINICAL STUDY. ACCORDING TO THE CLINICAL REPORT FORM, THE ALLOGRAFT WAS EXPLANTED APPROXIMATELY 5.5 YEARS AFTER IMPLANT DUE TO STRUCTURAL DETERIORATION, CALCIFICATION, VALVE LEAFLET DEGENERATION, INSUFFICIENCY, AND A TEAR OR PERFORATION OF VALVE LEAFLETS.<End Text>
1063481-2011-00030	INJURY	5/25/2011	INFORMATION REGARDING THE EXPLANT OF A SYNERGRAFT AORTIC VALVE AND CONDUIT ALLOGRAFT WAS OBTAINED THROUGH A RETROSPECTIVE CLINICAL STUDY. ACCORDING TO THE CLINICAL REPORT FORM, THE ALLOGRAFT WAS EXPLANTED APPROXIMATELY 10 YEARS AFTER IMPLANT DUE TO STRUCTURAL DETERIORATION, CALCIFICATION, VALVE LEAFLET DEGENERATION, STENOSIS OR OBSTRUCTION OF ALLOGRAFT VALVE AND CONDUIT.<End Text>
1063481-2011-00031	INJURY	5/25/2011	INFORMATION REGARDING THE EXPLANT OF A SYNERGRAFT AORTIC VALVE AND CONDUIT ALLOGRAFT WAS OBTAINED THROUGH A RETROSPECTIVE CLINICAL STUDY. ACCORDING TO THE CLINICAL REPORT FORM, THE ALLOGRAFT WAS EXPLANTED APPROXIMATELY 6 YEARS AFTER IMPLANT DUE TO STRUCTURAL DETERIORATION, CALCIFICATION, INSUFFICIENCY, OUTGROWTH OF ALLOGRAFT, AND A STENOSIS OR OBSTRUCTION OF ALLOGRAFT CONDUIT.<End Text>
1063481-2011-00032	INJURY	5/25/2011	INFORMATION REGARDING THE EXPLANT OF A SYNERGRAFT AORTIC VALVE AND CONDUIT ALLOGRAFT WAS OBTAINED THROUGH A RETROSPECTIVE CLINICAL STUDY. ACCORDING TO THE CLINICAL REPORT FORM, THE ALLOGRAFT WAS EXPLANTED APPROXIMATELY 3 YEARS AFTER IMPLANT DUE TO UNACCEPTABLE HEMODYNAMICS, CALCIFICATION, AND STENOSIS OF VALVE.<End Text>

Report Number	Event Type	Date Received	EVENT_TEXT
1063481-2011-00036	INJURY	6/17/2011	ACCORDING TO THE REPORT, A REOPERATION WAS REQUIRED ON A PATIENT WHO RECEIVED AN AORTIC VALVE AND CONDUIT SG ALLOGRAFT SIX YEARS AGO. THE SURGEON STATED THAT THE ALLOGRAF WAS VERY CALCIFIED AND IT WAS NOT AN EASY PROCEDURE. THE SURGEON EXPRESSED CONCERN WITH THE AMOUNT OF CALCIFICATION THAT WAS SEEN SIX YEARS POST-OPERATIVELY.<End Text>
1063481-2011-00039	INJURY	7/25/2011	AS PART OF THE CRYOVALVE SG AORTIC HUMAN HEART VALVE RETROSPECTIVE/PROSPECTIVE, MULTI-CENTER, COHORT STUDY (SGA0903.000), AN EXPLANT FORM INDICATING THE FOLLOWING EVENT WAS RECEIVED. ON 12/1/2008, THE PATIENT UNDERWENT AN EXPLANT PROCEDURE FOR THE FOLLOWING: UNACCEPTABLE HEMODYNAMICS; ALONG WITH CALCIFICATION, INSUFFICIENCY AND STENOSIS OR OBSTRUCTION OF ALLOGRAFT CONDUIT. THE ALLOGRAFT WAS EXPLANTED; HOWEVER, THE HOSPITAL INDICATED THAT THE EVENT WAS NOT RELATED TO THE FAILURE OF THE CRYOLIFE ALLOGRAFT.<End Text>
1063481-2011-00043	INJURY	8/11/2011	AS PART OF THE CRYOVALVE SG AORTIC HUMAN HEART VALVE RETROSPECTIVE/PROSPECTIVE, MULTI-CENTER, COHORT STUDY, AN EXPLANT FORM INDICATING THE FOLLOWING EVENT WAS RECEIVED. ON 6/30/2009, THE PATIENT UNDERWENT AN EXPLANT PROCEDURE FOR THE FOLLOWING: STRUCTURAL DETERIORATION; ALONG WITH CALCIFICATION, INSUFFICIENCY AND STENOSIS OR OBSTRUCTION OF VALVE. THE NATURE OF THE EVENT IS "ONE LEAFLET OF THE HOMOGRAFT DEMONSTRATED IMMOBILITY SECONDARY TO CALCIFICATION. THE OTHER TWO LEAFLETS WERE SCLEROTIC AND SOMEWHAT RESTRICTED. THE VALVE WAS REMARKABLY NON-FUNCTIONAL FOR AS WELL AS PT WAS DOING CLINICALLY." THE ALLOGRAFT WAS EXPLANTED.<End Text>
1063481-2013-00009	INJURY	3/5/2013	ACCORDING TO THE REPORT, THE SYNERGRAFT AORTIC VALVE AND CONDUIT ALLOGRAFT WAS IMPLANTED ON 07/15/2002. THE PATIENT HAS DEVELOPED SEVERE AORTIC REGURGITATION AND A TRANSCATHETER VALVE IN VALVE PROCEDURE IS PLANNED.<End Text>
MW1025725	INJURY	7/31/2002	UTILIZING INTERRUPTED 2-0 PLEDGETED SUTURES ON THE AORTIC SIDE, A #22 XENOGRAFT CRYOLIFE HOMOGRAFT WAS SELECTED AND SEWN IN PLACE PROXIMALLY. STITCHES WERE PLACED WITHIN 1 MM OF EACH OTHER TO OBTAIN THE BEST HEMOSTASIS POSSIBLE. FOLLOWING THIS, RIGHT AND LEFT CORONARY ARTERY BUTTONS WERE FASHIONED AND THEN SEWN OVER BUTTONS OF FELT TO THE HOMOGRAFT WITH RUNNING 5-0 PROLENE SUTURE. ADDITIONAL CARDIOPLEGIC SOLUTION WAS INFUSED AND THEN THE GRAFT WAS TAPERED AND SEWN DISTALLY OVER STRIPS OF FELT WITH RUNNING 3-0 PROLENE SUTURE. THE PT WAS REWARMED. THE AORTIC CROSSCLAMP WAS REMOVED. A SPONTANEOUS SINUS RHYTHM WAS FOUND. TEMPORARY ATRIAL AND VENT WIRES WERE PLACED. THE PT WAS WEANED FROM BYPASS WITH ADEQUATE HEMODYNAMICS. IT WAS NOTED THAT, DESPITE PROTAMINE SULFATE, THERE WAS STILL Oozing WHICH APPEARED TO BE IN THE NONCORONARY CUSP/ANT LEAFLET/AORTIC MITRAL CURTAIN AREA. DESPITE PLACING SEVERAL SUTURES FROM THE OUTSIDE, COMPLETE HEMOSTASIS WAS NOT OBTAINED. THEREFORE, THE PT WAS REHEPARINIZED, PLACED BACK ON CARDIOPULMONARY BYPASS, RECROSSCLAMPED, ADDITIONAL CARDIOPLEGIC SOLUTION WAS INFUSED. DISTAL ANASTOMOSIS WAS TAKEN DOWN AND THE HOMOGRAFT WAS THEN PLACED IN ANTERIOR LOCATION. THE GRAFT WAS THEN SUTURED, PT REWARMED, CROSSCLAMP REMOVED AND SINUS RHYTHM ENSUED. THE PT WAS WEANED FROM BYPASS ONCE AGAIN, BUT PERFECT HEMOSTASIS WAS NOT OBTAINED AND SO DECISION WAS MADE TO PLACE PT ON THE PUMP A THIRD TIME, TAKE OUT THE HOMOGRAFT AND REPLACE IT WITH A SECOND HOMOGRAFT. PT WAS REHEPARINIZED, PLACED BACK ON BYPASS, ETC AND SO THE PREVIOUS HOMOGRAFT COULD BE EXCISED. ALL THE STITCHES APEARED TO BE INTACT, BUT DESPITE THIS, THE PT CONTINUED TO BLEED. THERE WERE NO RENTS IN THE HOMOGRAFT AND NO HOLES THAT COULD BE ASCERTAINED. THE HOMOGRAFT WAS EXCISED AND A #21 XENOGRAFT HOMOGRAFT WAS SEWN IN PLACE ACCORDING TO PROCEDURE. PT WEANED FROM BYPASS A THIRD TIME AND ALTHOUGH, HEMOSTASIS WAS NOT PERFECT, EVENTUALLY WERE ABLE TO MAINTAIN AND GAIN HEMOSTASIS WITH BLOOD PRODUCTS.